AN EXPANDED ROLE FOR CLINICAL COORDINATORS IN INVESTIGATOR INITIATED CLINICAL TRIAL RESEARCH

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ABSTRACT

Clinical research is conducted to advance human medicine by developing efficacious treatments and improving patient outcomes when new therapies are developed and implemented. Clinical trials are a subset of the types of clinical research conducted on human volunteers in the development of new drugs, devices and other therapies. Prior to the start of a trial, a country's regulatory authority must review the trial to ensure it is scientifically and ethically sound. In Canada, the regulatory authority is Health Canada.

The International Conference on Harmonization (ICH) of technical requirements for the registration of pharmaceutics for humans aims to provide ethical and scientific quality standards for design, conduct, data collection and reporting in clinical trials. The Good Clinical Practice (GCP) Guidelines were created by the ICH Steering Committee to assure the public that rights, safety and well being of subjects are protected according to the Declaration of Helsinki, and the clinical data obtained in a ICH/GCP compliant clinical trial will meet regulatory requirements. Health Canada has adopted the ICH/GCP Guidelines and therefore, in Canada, all clinical trials involving humans must comply with these Guidelines.

The clinical trial coordinator is an important and central position on the research team executing many trial duties and communications. Regulatory authorities, Research Ethics Boards and the sponsor, overlook the role and responsibilities of a highly trained clinical coordinator, despite their vital and central position. The GCP Guidelines also fail to address the role and responsibilities of a clinical coordinator. Disconnect between guidelines, regulatory expectations and actual trial conduct provides an apparent need to formalize and clearly define the role and scope of a clinical coordinator. The Registered

Nurse (RN) brings professionalism, knowledge, skill and a holistic perspective to the expanded role of a clinical coordinator and to the clinical trial. Highly trained health professionals are capable of assuming more responsibilities and executing clinical trial design, setup and management as compared to the traditional administrative roles of the clinical coordinator. The expanded role of the clinical coordinator is especially beneficial for Principal Investigator initiated trials due to limited research personnel and resources.

Postoperative adhesions are a common complication following pelvic surgery, therefore, this clinical trial is relevant and a response to a healthcare need. My graduate studies focused on the development and set up of the clinical trial Protocol ADE002-2013 Phase I Trial of L-Alanyl-L-Glutamine for the Reduction of Peritoneal Adhesions in Adult Females Undergoing Myomectomy. My thesis is a discussion of general Canadian clinical trial research information followed by an explanation of how we executed the information to design and set up our PI initiated clinical trial. The value of the expanded role of the clinical coordinator as a member of the research team will also be discussed.

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To Shawn, thank you for being the calm in my storm. There were times where I thought I could not or did not want to finish. You have always encouraged me and helped me to realize my abilities and I love you for that.

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LIST OF ABBREVIATIONS

AE	Adverse Event
CAPA	Corrective Action Preventative Action
CCRP	Certified Clinical Research Professional
CIHR	Canadian Institute of Health Research
CPM	Conscious Pain Mapping
CPP	Chronic Pelvic Pain
CRF	Case Report Form
CTA	Clinical Trial Application
CV	Curriculum Vitae
D&C	Dilation and Curettage
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ESGE	European Society of Gynecological Endoscopy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GnRH	Gonadotropin Releasing Hormone
IACRN	International Association of Clinical Research Nurses
IB	Investigator's Brochure
ICH	International Conference on Harmonization

IRB	Institutional Review Board
IUA	Intrauterine Adhesions
JPMA	Japan Pharmaceutical Manufacturer Association
n	Sample Size
NOL	No Objection Letter
NSERC	Natural Science and Engineering Research Council of Canada
PI	Principal Investigator
RCT	Randomized Control Trial
REB	Research Ethics Board
RN	Registered Nurse
SAE	Serious Adverse Events
SBO	Small Bowel Obstruction
SCDM	Society of Clinical Data Management
SOCRA	Society of Clinical Research Associates
SOP	Standard Operating Procedures
SSHRC	Social Sciences and Humanities Research Council of Canada
TCPS	Tri-Council Policy Statement
TMF	Trial Master File
TPD	Therapeutics Product Directorate
UK	United Kingdom
WHO	World Health Organization
WMA	World Medical Association

CHAPTER ONE

INTRODUCTION

Clinical research is conducted to advance human medicine by developing efficacious treatments and improving patient outcomes when new therapies are developed and implemented. Clinical trials are a subset of the types of clinical research conducted on human volunteers in the development new drugs, devices or other therapies. Prior to the start of a trial, a country's regulatory authority must review the trial to ensure it is scientifically and ethically sound. In Canada, the regulatory authority for clinical research is Health Canada.

In all developed countries, clinical trials should be thoroughly evaluated and monitored to protect the health and rights of human volunteers and inspect the integrity of the study design. Rigorous and valid clinical trials are dependent on specific elements of study design. A randomized controlled trial (RCT) is the gold standard design for clinical trials. A double-blinded RCT, where the subject and the researchers are blinded to the treatment given to the subject, increases rigor and validity of the trial design by decreasing researcher and selection bias. Rigorous research design is essential for clinical trials because it provides scientific and ethical confidence to regulatory authorities, research ethics boards, clinicians and patients.

The Declaration of Helsinki is a statement of ethical principles for medical research involving human subjects developed by the World Medical Association (WMA) at the general assembly in 1964 (1). This statement has been amended nine times, lastly in October 2013 at the WMA general assembly in Brazil. The Declaration of Helsinki is

recognized by regulatory authorities and adopted by the clinical research industry for the protection of the human volunteers in clinical trials.

The International Conference on Harmonization (ICH) of technical requirements for the registration of pharmaceuticals for human use provides international ethical and scientific quality standards for designing, conducting, recording and reporting clinical trials. The ICH was formed because research-based industry and representing regulatory bodies recognized the need to harmonize guidelines and expectations of clinical trials in order to decrease duplication of research and to forward the development for new drugs. The ICH Good Clinical Practice (GCP) Guidelines aim to protect the human volunteers, decrease research and development costs and minimize the time it takes to market new efficacious therapies (2). The inception of ICH took place at a meeting in Brussels hosted by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in April 1990. Since then, 17 countries worldwide have adopted GCP guidelines to approve clinical trials and direct the clinical research industry.

In Canada, the federal regulatory authority is Health Canada's Therapeutic Products Directorate (TPD). This branch of Health Canada is in charge of reviewing the clinical trial applications (CTA), granting regulatory approval for clinical trial initiation, monitoring trial progress and adverse events (AE) and reviewing the safety, efficacy and quality of data prior to granting market authorization for new therapies. Health Canada's Guidance to Industry document contains the ICH GCP Guidelines and outlines how to comply with policies and governing statues and regulations (3). The document also provides researchers detailed instructions for developing and submitting a CTA to Health Canada's TPD.

The Tri-Council Policy Statement (TCPS) for ethical conduct for research involving humans is a joint statement by three Canadian agencies; the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Social Sciences and Humanities Research Council of Canada (SSHRC) (4). The statement aims to protect all human volunteers in Canadian research; however, Chapter 11 of the TCPS specifically addresses clinical trial research. The TCPS offers an online certification course for researchers, which is required by Canadian universities and research institutes. All individuals who wish to be involved in any aspect of human clinical research must complete the online course. The course can be accessed at http://www.pre.ethics.gc.ca/eng/education/tutorial-didacticiel/.

Traditionally clinical research trials are industry sponsored, initiated by pharmaceutical companies with the ultimate goal of market authorization. Investigator-initiated clinical trials are another type of trial where the PI is responsible for the design, setup and execution of the trial. The PI may seek out public funding such as government research grants or private funding such as a pharmaceutical company. In industry sponsored clinical trials the sponsor is ultimately responsible for overseeing, monitoring and auditing all trial conduct. In investigator-initiated trials, the PI assumes the role of the sponsor and is, therefore, responsible for all trial-related activities and conduct.

Canadian regulatory authorities, Health Canada's Therapeutic Products Directorate (TPD), require all clinical trials to function in accordance to the ICH/GCP guidelines. The ICH/GCP guidelines clearly outline the roles and responsibilities of the sponsor, PI, and REB in clinical research. Each section of the ICH/GCP guidelines addresses a specific research role and breaks down the responsibilities within this role.

The ICH/GCP guidelines are specific, detail-oriented and function as a valuable resource for clinical trial research personnel; however, the guidelines neglect the role of the clinical coordinator. With the rising numbers of clinical trials and the increasing demand for the expanded role of a clinical coordinator, ICH/GCP guidelines, other clinical research guidance documents, sponsors, PI and REB need to acknowledge and clearly define the roles and responsibilities of a clinical coordinator as part of the clinical research team.

CHAPTER TWO

RESEARCH QUESTION AND APPROACH

The roles of the clinical trial coordinator and research nurse are ambiguous and vary between research sites. Regulatory authorities, Research Ethics Boards (REB) and the Sponsor have neglected to define the roles and responsibilities of the clinical trial coordinator within their guidelines and regulations; consequently all the duties and responsibility are left with the Principal Investigator (PI). Therefore, we developed this project to address the issue of how a clinical coordinator with advanced education in clinical trials methodology could enhance the research team and help to stimulate investigator initiated clinical trials in a clinical department at the University of Saskatchewan's College of Medicine.

My study of the expanded role of the clinical coordinator in Principle Investigator initiated clinical trial research and addresses how the education, knowledge and experience of a RN with advanced education in the conduct of clinical trials can be of benefit to the many facets of a clinical trial. My study also addresses the importance of having clear roles and responsibilities for the clinical coordinator and outlines why regulatory authorities, REB and the Sponsor should acknowledge and include the clinical coordinator's roles and responsibilities in guidelines and regulations.

My graduate studies experiences are based on the set up and development of the clinical trial Protocol ADE002-2013 A Phase I Trial of L-Alanyl-L-Glutamine for the Reduction of Peritoneal Adhesions in Adult Females Undergoing Myomectomy. The study was an investigator-initiated clinical trial using an investigational product developed by a local Saskatoon company. The PI, Dr. Donna Chizen, approached the

sponsor when she learned of the drug as a novel treatment for adhesion formation by a surgical resident's research presentation. The PI chose to investigate the application of the drug in gynecological surgeries because postoperative adhesions are a common complication following pelvic surgery. The potential for L-Alanyl-L-Glutamine to prevent postoperative adhesions carries significant clinical value with the potential of a new standard of care for prevention of postoperative adhesion formation. The PI created a research team to execute a pilot clinical trial to investigate the potential role of the new compound in a standardized gynecologic surgical procedure. I joined the team as the clinical coordinator and the investigation team found this an ideal opportunity to provide advanced education in a critical aspect of the conduct of clinical trials. It was deemed an appropriate venue for exploring an advanced and expanded role for an RN clinical coordinator to facilitate the development of increased investigator-initiated clinical trial activity in the University of Saskatchewan College of Medicine.

Following a review of the literature on postoperative adhesions, each chapter in this thesis is divided into two parts; 1) a theoretical explanation and discussion of each clinical trial topic and 2) how we executed the information to set up the clinical trial. There is limited literature on the roles and impact of the clinical coordinator in clinical research trials. The research team, including the PI and myself, used the clinical research trial environment of ADE001 & ADE002 research protocols to develop what we believe is the first study to critically analyze the expanded role of the clinical coordinator and its value in an investigator-initiated trial. I worked with the PI and research team to develop the clinical trial design, obtain approval and site set up for patient enrollment according to ICH/GCP guidelines. In Chapter Three, I will review the literature on post-operative

adhesion formation to set up how the biological hypothesis is tested. The clinical trial protocol synopsis is presented in Chapter Four to outline the clinical trial that was used as a foundation for my experiential learning and to illustrate how my work helped the PI and research team to address and execute the investigator-initiated trial. In the proceeding chapters, I will describe the clinical trial process as it related to my advanced education in obtaining approval for an investigator-initiated clinical trial. Chapter Five will describe the phases of clinical research trials as well as study design. Chapter Six will address the ethics of clinical research, specifically in Canada. Chapter Seven will outline the requirements for a Health Canada Clinical Trial Application. Chapter Eight will describe the ICH/GCP guidelines as they apply to clinical trial documents and site setup. Chapter nine will discuss the roles of the sponsor and PI as outlined by Canadian regulations and ICH/GCP guidelines. The roles, responsibilities and value of the clinical coordinator in an expanded role will also be discussed. The information presented throughout my thesis will address my research questions; how can the education, knowledge and experience of a RN benefit a clinical trial; what is the importance of having clear roles and responsibilities for a clinical coordinator in an expanded role; and why should regulatory authorities, REB and sponsors acknowledge and include the clinical coordinator role in guidelines and regulations?

CHAPTER THREE

LITERATURE REVIEW

3.1 Postoperative Adhesions

Postoperative adhesions are a frequent byproduct and complication of abdominal surgery; adhesions can result from infection, ischemia and foreign body reaction, and occur most commonly after any surgical procedure. Abdominal and pelvic surgeries are the most common cause of peritoneal adhesions and remain a source of considerable morbidity. Adhesions are especially prevalent following gynecological surgery (5). Varying incidence rates of postoperative adhesions have been reported. The incidence of adhesions is approximately 93% following general surgical abdominal operations and may be as high as 100% following gynecologic operations (6-8).

There are 3 different types of post-operative adhesions: 1) adhesion formation (formed at surgical site); 2) de novo adhesions (formed at non-surgical site); and, 3) adhesion reformation (reformed following surgical lysis) (9). It has been generally believed that laparoscopic procedures result in fewer de novo adhesions when compared to laparotomy (10). However, no significant differences were observed in de novo adhesion formation following laparoscopic and laparotomy surgeries in a recent meta-analysis (11).

Complications occurring as a result of the formation of adhesions are comparable between laparoscopic and laparotomy surgeries (12). The most common complications of postoperative adhesions are small bowel obstruction, pelvic pain and female infertility (13, 14). Morbidity caused by adhesions also has economic consequences. Adhesion-related complications lead to longer hospitalization. Morbidity related to post-operative

adhesions may require re-hospitalization up to 10 years after the initial surgery (12, 15). Pre-existing adhesions make subsequent surgeries more challenging, take longer to complete and often result in adhesion reformation (10).

Complications and consequences of postoperative abdominal and pelvic adhesions are outlined in the medical literature; however, the pathophysiology of adhesion formation and methods of adhesion prevention are controversial. New scientific theories on the development of post-operative adhesions are being studied and developed. Some of the more novel theories are built on the body's inflammatory response to injury, oxidative stress or improper wound healing.

3.2 Pathophysiology of Adhesions

The intra-abdominal and pelvic organs are contained within the peritoneal cavity and are encased by a highly vascularized epithelial membrane termed peritoneum. The main function of the peritoneum is to protect the organs, blood vessels and lymph within the abdomen (16). Damage to the peritoneum may result in adhesion formation. Adhesions are defined as abnormal deposits of fibrous tissue that form within the peritoneal cavity.

The exact mechanisms of adhesion formation are poorly elucidated. Adhesions form as a result of abnormal wound healing and fibrous repair following peritoneal injury and involve various complex biochemical and mechanical processes (17, 18). Peritoneal injury is most often caused by surgery, infection and/or foreign body reactions (sterile glove powder, surgical gauze, sutures, and irrigation fluids). These insults trigger a disruption of stromal mast cells that release vasoactive substances such as histamines and kinins (5). Increased capillary bleeding and the release of vasoactive substances after

tissue injury cause increased peritoneal vascular permeability and exudation of fibrinogen (19). Injury and bleeding activate the coagulation cascade, thrombin forms which triggers the conversion of fibrinogen to fibrin (9). In ideal healing conditions, fibrin is reabsorbed by fibrinolysis and normal peritoneal wound healing occurs with no adhesion formation (17). Fibrinolysis is the dissolution of thrombi. If fibrinolysis does not occur within three to five days after trauma, collagen-secreting fibroblasts infiltrate and deposit extracellular matrix (20). Microvascular structures, such as arterioles, venules and capillaries form within the fibrous bands resulting in the production of adhesions.

Fibrinolysis may not occur for two primary reasons. First, ischemic injury leads to tissue damage and vascular insufficiency. Inadequate blood and oxygen supply inhibit fibrinolysis (8, 9, 17). Adhesions quickly develop to prevent further ischemia. Second, inflammation mediates recruitment of proteins, cytokines, macrophages, platelets, lymphocytes and mesothelial cells; aberrant wound healing and subsequently, adhesion formation occurs following the inflammatory response.

Macrophages are highly adaptable cells involved in the initiation, maintenance and resolution of inflammation (21). Postoperatively, macrophages increase in number and alter in function. Macrophages observed following surgical intervention differ from resident peritoneal macrophages and contribute to peritoneal remesothelialization in the injured area (18). New findings are leading researchers to hypothesize that repair cells foreign to the peritoneal cavity and recruited due to injury and inflammation in the peritoneal cavity create adhesions as a means of immediate repair. The mechanism of the varying cells involved in wound healing following injury and peritoneal adhesion formation require additional studies. Future research into the mechanism of adhesion

formation may lead to efficacious therapies for the prevention and/or treatment of peritoneal adhesions.

3.3 Complications of Postoperative Adhesions

3.3.1 Small Bowel Obstruction

Small bowel obstruction (SBO) is a common complication of adhesion formation after abdominal and pelvic surgery. SBO occurs when adhesions develop around and/or within the small bowel and create a blockage of the intestinal track. Approximately half of SBO are due to post-operative adhesions (22). Intra abdominal gynecological procedures, appendectomies and colorectal resections are the most common surgeries that are associated with adhesions formation and consequently with SBO. Surgeries done by open laparotomy are responsible for twice as many adhesive obstructions than surgeries done using laparoscopy (23). Over the past 25 years, 1.8% of all hospital admissions were due to SBO. Slightly more than half of the admissions are thought to be caused by post-operative adhesions (6). In one study, 74% of SBO cases in adults and 30% of hospital re-admissions were due to post-operative adhesions (24). The incidence of both SBO and adhesiolysis have not changed significantly in over two decades despite an increase in the number of laparoscopic procedures and the availability of adhesion preventing pharmaceutical therapies.

3.3.2 Chronic Pelvic Pain

Chronic pelvic pain (CPP) is a common problem in women and accounts for more than 10% of all outpatient gynecological visits and 40% of diagnostic laparoscopies (25, 26). Chronic pain is most often defined as symptoms lasting for 6 months or more (26).

Post-operative adhesion formation as the cause of CPP is a controversial phenomenon with unknown etiology. The condition presents as continuous or intermittent and/or colicky pain. Continuous pain is believed to be caused by adhesions retracting the viscera without obstruction, while colicky pain is due to partial obstruction (27).

Adhesiolysis by laparoscopy is frequently used to treat CPP secondary to post-operative adhesions. A prospective study on the effectiveness of adhesiolysis was conducted (28, 29). Two hundred twenty four patients with CPP who had previously undergone at least one surgical procedure were recruited. After 3 months, 74% of patients reported being pain free or experiencing less pain. Five percent of the patients in this study underwent open laparotomy to correct a bowel perforation and 10% of patients had a second-look laparoscopy for recurrent pain after an average of 16 months. De novo adhesions were found in 20% of women who underwent a second-look laparoscopy. The results of this study may be interpreted to mean that adhesiolysis is not an effective treatment for CPP on a cost-benefit basis.

Conscious pain mapping (CPM) is another method of CPP diagnosis and treatment. In this diagnostic algorithm, laparoscopy is done under local anesthetic which allows for the surgeon to manipulate the adhesions and the patient to report which adhesions or sites cause pain (30). It has been theorized that CPM may help discover sites of pelvic pain that were unable to be diagnosed using traditional laparoscopy (31). CPM may help to lower the number of surgical sites and correspondingly reduce the associated potential risk to the patient.

3.3.3 Female Infertility

Adhesions are the leading cause of secondary infertility in women (10). Female infertility can be caused by peritoneal, tubal or intrauterine adhesions. Infections such as gonorrhea, chlamydia and pelvic inflammatory disease may cause pelvic and tubal adhesions if left untreated (32, 33). It has been reported that patients who underwent adhesiolysis had pregnancy rates of 32% after 12 months and 45% after 24 months compared to women who did not undergo adhesiolysis, 11% and 16% respectively (34). In another study, 100 subjects underwent laparoscopy to determine the etiology of primary infertility (35). Seven percent of the subjects had pelvic adhesions and 1% had peritubal adhesions. In a larger case series, twelve hundred subjects in Bangladesh underwent laparoscopic evaluation to characterize infertility; 16% had peritubal adhesions causing infertility and 17% required adhesiolysis (36). Similar results from another study found adhesions in 27% of subjects who underwent diagnostic laparoscopy for infertility (37). In a meta-analysis, pregnancy rates were studied in 1004 women after surgical or medical treatment for inflammatory bowel disease (38). Pregnancy rates were significantly lower in women who underwent surgery compared to women who were treated medically.

Ectopic pregnancies may cause pelvic and tubal adhesions and pre-existing adhesions may lead to repeat ectopic pregnancies. Surgical treatment of ectopic pregnancies is associated with decreased rates of intrauterine pregnancy compared to chemical treatments such as methotrexate (39). Subsequently, this observation has been interpreted to mean that surgically induced adhesions may further complicate the presenting problem.

Intrauterine adhesions (IUA) are defined as adhesions that partially or completely obliterate the endometrial cavity, the internal cervical os, and/or the cervical canal (40). The most common etiologies for IUA are: vacuum aspiration, dilation and curettage (D&C), cesarean section and myomectomy. In a prospective study, 63 patients who had undergone one of the above procedures were observed for the subsequent 5 years. The overall postoperative pregnancy rate was 44%. Women with intra cavitary uterine adhesions who had vacuum aspiration were observed to have the highest pregnancy outcomes while women who had D&C experienced the lowest pregnancy outcomes.

Some researchers have hypothesized that women who have had cesarean sections have lower rates of postoperative adhesion formation than found following other obstetrical or gynecological surgeries (41). Demonstrating adhesion trends following cesarean section is difficult because second-look surgery is not always clinically and ethically warranted. Retrospective studies and chart reviews of women undergoing repeat cesarean sections are the most common way post-operative adhesions rates are observed and reported. Adhesion formation following cesarean sections can increase surgical difficulty for subsequent cesarean section. Adhesion formation from previous cesarean sections increased surgical difficulty and restricted surgeons from conducting bilateral tubal ligations in 2% of patients scheduled for a tubal ligation at time of repeat cesarean section (42). Obstetrical complications of post adhesion adhesiolysis at the time of repeat cesarean sections may include hemorrhage, emergency hysterectomies or mortality. In the United States, cesarean section rates account for approximately 33% of all births (43). In Canada during 2011 and 2012, 18% of women underwent primary cesarean sections, while 83% of women who had a previous cesarean section underwent

repeat cesarean sections (44). The World Health Organization (WHO) recognizes an overuse of cesarean sections with no improvement in neonatal outcomes above a 15% cesarean section rate (45). In Brazil, approximately half of all deliveries from 2008 to 2012 were by cesarean section (46). Other countries such as Dominican Republic and Iran follow closely behind with cesarean section rates that are above 40%. Studies examining the extent, severity and morbidity of adhesions following obstetrical surgery are required for improved clinical and surgical decision-making due to the global increase of cesarean section. Further research is needed to discern the causative relationship of adhesions, infertility and pregnancy rates as a result of infertility treatment and/or adhesiolysis. Comparison of different types of pelvic surgeries (myomectomy versus hysterectomy), modes of surgery (laparoscopic versus laparotomy versus transvaginal), adhesion development and pregnancy rates will provide better experimental models and help guide clinical decision-making.

3.4 Postoperative Adhesion Prevention

Adhesion prevention is the responsibility of every surgeon. Recognition and awareness of adhesion prevention may lead to improved surgical diligence. An adhesion awareness survey was conducted among gynecologists in the United Kingdom (UK). The survey results were interpreted to mean that surgeons require further education and awareness on the implications of post-operative adhesions and that most surgeons are not routinely counseling patients on the risks of adhesions during the consent process for their surgical procedure (47). The Expert Adhesions Working Party of the European Society of Gynecological Endoscopy (ESGE) consensus proposal states, “Adhesions need to be recognized as the most frequent complication of abdominal surgery” (10).

3.4.1 Surgical Techniques

Pelvic and abdominal adhesion research is extensive; yet, the pathophysiology of adhesion formation and how to prevent the development of adhesions remains unknown. Surgical technique is consistently highlighted as an important part of adhesion prevention and/or reduction. Gentle tissue handling, good hemostasis and minimizing ischemia are overall good surgical practice and crucial for adhesion prevention (48). Eliminating, or reducing, the introduction of foreign bodies into the surgical site or surrounding anatomy helps to decrease adhesion formation. Traces of starch from gloves and lint from packs and drapes have been found in adhesions at second-look laparoscopy (9). Decreasing unnecessary tissue frequently drying during surgical procedures and irrigating tissues can also help prevent adhesions.

Adhesion rates have been compared among laparoscopic and laparotomy surgeries (49). Women who underwent laparoscopic surgery had significantly fewer adhesions at the operative site than women who underwent laparotomy (50). Similarly, when cholecystectomies performed laparoscopically or by laparotomy were compared, all patients who underwent laparotomy had thick, extensive adhesions; whereas 28% of the laparoscopic group developed loose adhesions that were easy separable (51). In another study, there was no significant difference in adhesions between laparoscopic and laparotomy surgeries; however, women in the laparotomy group reported higher rates of pelvic pain (52). The incidence of intra-abdominal adhesions ranged from 70% to 90% in an autopsy study involving patients who had prior laparotomy (53).

Different suturing techniques may have an effect on post-operative adhesions. Suturing technique is often the choice of the surgeon and commonly based on best

practice. Adhesion rates were assessed in single layer and double layer closure of the uterine wall in 127 women who had repeat cesarean sections (54). Twenty-four percent of the single layer group and only 7% of the double layer group developed extensive adhesions to the bladder following their first cesarean. Other pelvic adhesions were present in both groups, although there was no significant difference between the single layer and double layer groups. Adhesions to the bladder increase surgical difficulty, as the surgeon must remove the adhesions and separate adhesions from the bladder to any adjacent tissue, which may thereby increase the risk of bladder injury.

Suturing the peritoneum at the time of closing the abdominal incision during a cesarean section is optional and determined by the surgeon. Suturing the peritoneum versus not suturing the peritoneum may have implications for postoperative adhesions formation; however, study data are inconsistent in the literature. One patient with peritoneal closure had significant pelvic adhesions at the time of repeat cesarean section compared to 17 with no peritoneal closure (55). In another study observing peritoneal versus no peritoneal closure, no significant differences were observed in adhesion severity and extent among 97 women who had repeat cesarean sections (56). Similarly, peritoneal closure had no significant effect on adhesion development and severity in a systematic review of three studies (57). Currently, post-operative adhesions appear to be inevitable despite good surgical practice and techniques to help decrease adhesion formation.

3.4.2 Current Therapies

The efficacy and use of commercial products for the reduction of postoperative adhesions are debated among researchers and surgeons. Various methods of adhesion

prevention have been marketed. They include, but are not limited to, prevention of fibrin deposition in the peritoneal exudate, reduction of local tissue inflammation and removal of fibrin deposits (58). Most of the existing methods inhibit only one mechanism and have had limited success. Physical barriers used to prevent adhesion formation include implants made of resorbable fabrics or membranes. Gels formed of biocompatible materials have also been employed to reduce adhesion formation. INTERCEED® (Ethicon, Inc.) and SEPRAFILM® (Genzyme Biosurgery, Inc.) are the only two barrier products currently approved by the FDA for post-operative adhesion formation. Both products had approximately a 50% efficacy rate in pre- and post-market clinical trials. There is no current standard of care for the prevention of post-operative intraperitoneal adhesion formation.

3.4.2.1 INTERCEED®

INTERCEED® is a fabric composed of oxidized, regenerated cellulose. INTERCEED® is marketed by Ethicon, a division of Johnson & Johnson. The United States FDA (Food and Drug Administration) has approved this absorbable adhesion barrier for use in laparotomy gynecological procedures; however, INTERCEED® is not approved for laparoscopic procedures. INTERCEED® can only be placed in the body once meticulous hemostasis has been achieved and cannot be used as a hemostatic agent. Placement of the fabric is crucial for the efficacy of the product. Surgeons determine the placement based on where they think adhesions most are likely to form. A complication related to the INTERCEED® placement, INTERCEED® itself may cause adhesion formation if the fabric is folded, layered or joined to adjacent tissues (59). The fabric

must be discarded if it comes into contact with blood. Each piece of fabric costs approximately $175 US, which may present an economic challenge.

In a multicenter, Randomized Controlled Trial (RCT) study, 55 patients with bilateral ovarian disease were treated with INTERCEED® (60). At the time of surgery, only one ovary was wrapped with INTERCEED®. A second-look procedure was done 10 to 98 days later and significantly fewer adhesions were found in the patients treated with INTERCEED®. The ovaries were the surgical target site for the application of the fabric and assessment of adhesions, which may have added strength to the statistics and could be perceived as a bias to the study. In addition, no comments or data were noted for other peritoneal adhesions that may have formed due to surgery. Placement of the fabric may be more complicated in cases where numerous anatomical structures (ovaries, tubes, uterus) are affected. In a study in which twenty-eight women underwent adhesiolysis for infertility or CPP, half of the pelvis was treated with INTERCEED® and the other half served as an internal control (61). The side treated with INTERCEED® had significantly fewer adhesions than the control upon second-look laparoscopy. It is also important to note that the study targeted and assessed a specific anatomical site and did not mention adhesion formation or reformation to other tissue or organs.

3.4.2.2 SEPRAFILM®

SEPRAFILM® is another absorbable adhesion barrier composed of chemically modified sodium hyaluronate/carboxymethylcellulose. SEPRAFILM® is FDA approved for use in pelvic and abdominal laparotomies; however, it is not approved for use in laparoscopy. SEPRAFILM® acts as a temporary bioresorbable barrier separating tissue surfaces to enable normal tissue repair (62). The SEPRAFILM® membrane becomes a

hydrated gel in 24 to 48 hours, is slowly reabsorbed within one week and is excreted from the body in less than 28 days. Surgical handling can be difficult due to the stiff and sticky nature of the membrane. Because SEPRAFILM® can increase the incidence of abdominal abscess and anastomic leak, it therefore must not be wrapped around suture or staple lines (63). In an efficacy study, women treated with SEPRAFILM® had a lower incidence of de novo adhesion formation in 3 of 23 abdominopelvic sites evaluated compared to a placebo group (64). SEPRAFILM® is an adhesion prevention agent that has received the greatest research attention. Although SEPRAFILM® has a slightly higher efficacy rate than INTERCEED®; some surgeons continue to argue the effectiveness of SEPRAFILM® and its mechanism of action (65).

3.4.2.3 ADEPT®

ADEPT® is an adhesion barrier solution composed of 4% icodextrin. Icodextrin is a colloid osmotic agent commonly used as an aqueous solution. ADEPT® is marketed by Baxter and has been approved by the FDA for use in gynecological laparoscopic procedures. When placed in the peritoneal cavity ADEPT® provides temporary separation of peritoneal surfaces by hydroflotation as a result of maintaining a fluid reservoir within the peritoneal cavity for 3 to 4 days (66). Icodextrin has a safety profile similar to Ringers Lactate solution (67). It is also a vehicle for peritoneal dialysis when used at a 7% concentration (68). There are scant data to support the efficacy of ADEPT® in post-operative adhesion prevention. However, surgeons report that ADEPT® is easy to administer and is well tolerated by patients (69).

3.5 Myomectomy

3.5.1 Uterine Fibroids

Uterine fibroids (myomas) are a common disorder in women during their reproductive years with an incidence of 20% to 50% (70). Uterine fibroids increase the size of the uterus and may lead to menorrhagia, dyspareunia, urinary frequency and incontinence. Uterine fibroids have been associated with pelvic pain as the fibroids and uterus create pressure on adjacent pelvic and abdominal structures (71). Uterine fibroids also have fertility implications when fibroids compress the tubal ostia, restrict uterine expansion and distort the endometrial cavity, although a cause and effect relationship has not been established. Typical therapies for uterine fibroid related complaints include hormonal therapies to regulate menstruation, gonadotropin releasing hormone agonist therapy (GnRH) to reduce the size and vascularity temporarily, myomectomy completed by laparoscopic or open laparotomy surgery, uterine artery embolization and hysterectomy (72). Myomectomy is preferred when there is a desire to preserve fertility or as a personal choice to avoid hysterectomy and its potential complications (73, 74). Uterine myomectomies performed laparoscopically or at laparotomy require that an incision be made through the uterine serosa to expose the underlying fibroid for excision. Following the myomectomy, intramural suturing is typically needed to reapproximate the remaining uterine muscle. Suturing is also completed to reapproximate the edges of the incised uterine serosa to decrease the formation of adhesions.

3.5.2 Myomectomy and Adhesions

Myomectomies result in some of the highest rates of postoperative adhesions observed following gynecological surgical intervention (75). Postoperative adhesion

formation following myomectomy with, and without, the use of an anti-adhesion agent has been extensively researched. Surgical technique designed to prevent or reduce adhesion formation is emphasized in each study. In one study, postoperative adhesion formation and location of uterine incisions were compared in infertile women (34). On second look laparoscopy, women with incisions made on the posterior wall of the uterus had significantly more adhesions (97%) than those with anterior wall or fundal incisions (55%). Any adhesions present at the time of second-look laparoscopy were removed. Pregnancy rates following myomectomy and adhesiolysis were 33% at 6 months and 67% at 12 months. In a subsequent study, the number of myomas and diameter of the largest myoma enucleated were significant factors in extent and severity of the adhesions formed at the uterine incision at second-look laparoscopy following myomectomy (73). More studies and data of this nature may help capture the post-operative adhesion forming trends following myomectomy to aid in standardizing surgical technique(s). For patients who have multiple or large myomas enucleated, a second-look laparoscopy and adhesiolysis may be beneficial.

3.5.3 Clinical Research

Myomectomy is a good surgical model for clinical research in postoperative adhesion prevention due to its adhesiogenic nature. Second-look laparoscopy is the gold standard for post procedure adhesion assessment. At the second look laparoscopy, adhesions formed recently can be lysed (76). Some surgeons will routinely do a second-look laparoscopy following myomectomy. A second-look procedure is beneficial to the patient, especially when the indication for primary surgery is treatment for infertility. Myomectomies performed by laparoscopy and at laparotomy were compared with, and

without, an oxidized regenerated cellulose adhesions barrier (77). Both laparoscopic and laparotomy groups had significantly fewer adhesions with the use of the barrier at the time of surgery compared to those groups who underwent surgery without the barrier. Adhesions in the barrier groups were filmy compared to the strong, cohesive adhesions found in the non-barrier groups. Myomectomy was the surgical model of choice in a prospective, randomized, blinded, multicenter SEPRAFILM® trial (78). Women treated with SEPRAFILM® had fewer adhesions and the extent and severity of adhesions that were present were less than the number of adhesions in women who were not treated with SEPRAFILM®. However, adhesion formation remains a challenge following uterine surgeries despite existing adhesion preventing agents and related studies showing significance (77).

3.6 Conclusion

Postoperative adhesions are currently an inevitable consequence of surgery and morbidities such as small bowel obstruction, pelvic pain and female infertility may occur because of the formation of adhesions. Morbidities related to postoperative adhesions increase hospital stays and/or require further treatment, and present physical challenges to patients requiring surgical intervention. Adhesions occurring as a result of surgery are an economic burden to the healthcare system. Because of the high incidence of adhesions following surgery, surgical technique designed to decrease potential adhesion formation should always be practiced. Increasing awareness of post-operative adhesions and implementing practices are required to help reduce the formation of post-operative adhesions. In addition, patients should be educated about the risk of adhesion formation at the time of consent prior to surgery.

The precise pathophysiology of postoperative adhesions remains unknown. The commercially available adhesion preventing agents address different aspects of the theories of adhesion formation. Presently, there is no adhesion prevention therapy approved for both laparotomy and laparoscopy surgeries. Barrier technologies for adhesion prevention are the most popular and efficacious agents currently available and offer less than a 50% rate in adhesions prevention. None of the commercially available products address the underlying mechanism of peritoneal inflammation.

Further research is needed to identify the etiology of postoperative peritoneal adhesions and develop a novel therapy with improved rates of adhesion prevention/reduction. Second-look laparoscopy remains the gold standard to assess extent and severity of adhesions following intervention. Myomectomy should be considered as a surgical model in future adhesion prevention research due to its high adhesion rates. Second look laparoscopy should be adopted as the standard method to evaluate adhesion prevention following surgery designed for fertility preservation or treatment.

CHAPTER FOUR

CLINICAL TRIAL PROTOCOL SYNOPSIS

4.1 Study Number and Title

ADE002-2013: A Proof of Concept Study of L-Alanyl-L-Glutamine for the Reduction of Peritoneal Adhesions in Adult Females Undergoing Myomectomy. This is a Phase I clinical trial.

4.2 Study Objectives

To test the null hypothesis that there is no significant difference in the extent and severity of adhesions following myomectomy in patients treated with L-Alanyl-L-Glutamine or placebo by peritoneal cavity administration.

To establish preliminary safety and tolerability of a formulation of L-Alanyl-L-Glutamine in Water for Injection, pH= 6, or placebo administered into the peritoneal cavity in humans at a dose of 1g/kg of body weight.

4.3 Endpoint

The primary endpoint will be the observation of fewer adhesions observed in the L-Alanyl-L-Glutamine treated group compared to placebo at 6-8 weeks post-myomectomy. Based on the analysis approach outlined in the Protocol Section 11.0 Study Variables and Statistical Analysis, the primary endpoint will be met if the treatment group has fewer patients in the adhesions category compared to the placebo group.

4.4 Study Design

Potential subjects will have a diagnosis of uterine fibroids (myoma) and will plan to have myomectomy surgeries for medical indications, (not because of study participation). Eligibility to participate in the study will be determined according to inclusion/exclusion criteria. Informed consent will be obtained according to the GCP and TCPS guidelines. Thirty-eight subjects will undergo a laparoscopic myomectomy and 10 subjects will undergo a myomectomy by laparotomy. All myoma diagnosis will be confirmed using ultrasound examinations. The method of surgery will be determined by their surgeons' clinical judgment and will be based on the subject's medical and /or surgical needs and concerns. Reasons for opting for a laparoscopic or laparotomy approach may depend upon numerous factors such as, the medical suitability for laparoscopic surgery, the size of the myomas within the uterus and the location of myomas within the pelvis and abdominal cavity. Subjects will be randomly assigned to treatment (L-Alanyl-L-Glutamine) or placebo within each surgical method group. At the time of surgery, treatment (L-Alanyl-L-Glutamine) or the placebo will be delivered into the peritoneal cavity. The primary myomectomy surgery will be followed by standard hospital post-operation care. A follow-up laparoscopic evaluation will be done 6-8 weeks post-operation to determine the efficacy of the treatment (L-Alanyl-L-Glutamine). The study duration will be approximately twelve (12) months from first patient, first visit to last patient, last visit.

4.5 Study Population

The sample size for this study is n = 48. Twenty-four subjects will receive the treatment (L-Alanyl-L-Glutamine). Twenty-four subjects will receive the placebo. Ten

subjects, 5 subjects receiving treatment and 5 subjects receving placebo, will undergo a myomectomy by laparotomy. The remaining 38 subjects will undergo a laparoscopic myomectomy.

4.5.1 Inclusion Criteria

- Subjects are female
- Subjects are 18 years of age or older at the time of consent
- Subjects have a BMI between 17-40
- Subjects must have signed informed consent form
- Subjects have a preoperative diagnosis of uterine fibroids and plan to have a myomectomy completed surgically as part of their standard care
- Subjects must have a physical examination and compliance assessment

4.5.2 Exclusion Criteria

- Subjects whose BMI is outside the range of 17-40
- Subjects participating in another clinical trial with a drug or device
- Subjects who have participated in a clinical trial with a drug or device within 30 days prior to this study
- Subjects with suspected or diagnosed pregnancy
- Subjects with undiagnosed vaginal bleeding
- Subjects with suspected intraabdominal infection
- Subjects who are immunocompromised
- Subjects diagnosed with cancer

- Subjects treated with hemostatic agents (e.g. fibrin sealant, collagen, oxidized cellulose)
- Subjects treated with adhesion prevention agents other than this study's investigational product (e.g. Intergrel® Adhesion Prevention Solution, Seprafilm® Membrane)
- Subjects taking anti-epileptic medications
- Subjects who have been treated or are being treated with Methotrexate or other chemotherapeutics agents
- Subjects with an American Fertility Society score of Stage D at the time of myomectomy, as determined by the surgeon at the primary surgery

4.6 Study Treatment

The active substance is L-Alanyl-L-Glutamine. It enhances wound healing and plays a role in stress response through muscle repair, maintenance of digestive health, and in the modulation and function of neutrophils, macrophages and lymphocytes.

4.6.1 Dosing

The treatment will be dosed at 1g/Kg body weight of L-Alanyl-L-Glutamine, applied to the peritoneum at a concentration of 400mg/mL in water for injection (WFI), pH=6, 20mL in a 20mL vial.

4.6.2 Safety

Based on rat studies, in which the product L-Alanyl-L-Glutamine, formulated as described above and dosed in the range of 0.3g/kg of body weight to 1.5g/kg of body, no toxicities or adverse effects at any of the doses tested were observed. In humans, L-

Alanyl-L-Glutamine is a well-characterized nutritional supplement. It has been used widely in Total Parenteral Nutrition and has been dosed parenterally and enterally in a hospital setting in critically ill patients with no adverse effects noted.

4.6.3 Efficacy

The ability of the product L-Alanyl-L-Glutamine to reduce post surgical adhesions as proposed above will be determined during the 6-8 week post-operation follow up laparoscopic examination. Both the incidence and the severity of adhesions will be assessed. The incidence of adhesions will be determined visually. Digital recording of all surgeries and sites where the uterine surface was opened/incised/cauterized/sutured will be compared between first and second surgeries. Severity of the adhesions will be assessed using the AFS (American Fertility Society) scoring system, which evaluates the extent and aspect of adhesions at four anatomical sites, right ovary, right fallopian tube, left ovary, left fallopian tube. All findings will be recorded in the subject's case report form (CRF).

CHAPTER FIVE

CLINICAL RESEARCH TRIALS

5.1 Phases of Clinical Trials

The United States (US) Federal Drug and Food Administration (FDA) classifies pharmaceutical development into four phases, each with specific endpoints (3). The four phases, by definition, are mutually recognized by numerous regulatory agencies, simplifying multi-center trials conducted in different countries. The goal of a Phase I trial is to establish the safety profile of a drug by evaluating the pharmacokinetics and pharmacologic effects (79). Phase I trials, sometimes referred to as "first in man", are the first investigation of a new drug in humans, most commonly healthy volunteers. In some areas of clinical research where it is unethical to administer a drug to healthy volunteers Phase I may be trialed in patients. Common examples are cytotoxic substances such as chemotherapy or antiretroviral type drugs. Phase II clinical trials are designed using Phase I data to evaluate the drug's efficacy in patients with a medical condition. Phase II trials may also be referred to as proof of concept studies where the drug's mechanism of action in humans may be determined or validated. Most often Phase II clinical trials involve a control group(s) given a placebo or another commercially available pharmaceutical as a comparator. Side effects and other risks associated with the drug are determined in phase II trials. Studies that use commercially available drugs investigated under a new indication are also classified as Phase II trials. Phase III clinical trials follow Phase II trials that have demonstrated efficacy and warrant further study and investment. Phase III trials are multi-center studies with large sample sizes. In the pharmaceutical industry, Phase III trials are referred to as a pivotal trial because study outcome may be

utilized to apply to the regulatory authority for market authorization. In Canada, this is called a New Drug Submission and must be filed with Health Canada's Therapeutic Products Directorate (TPD). All studies that are conducted once a drug has received market authorization are considered Phase IV trials. Phase IV trials can be any type of study provided it is within the approved indication and has clear scientific objectives. Common Phase IV studies involve safety, morbidity/mortality and epidemiological endpoints.

5.2 Research Design

5.2.1 Sample Size

Sample size refers to the number of subjects recruited into a study. Sample size (n) represents a portion of the population (N) being studied. Appropriate sample size is important in order to obtain accurate information on the population and/or intervention being studied (80). The data obtained from the number of subjects recruited provides a sample mean, which represents the mean of the population (81). The standard error of the mean indicates the amount of error that may occur when a random sample is used as a predictor of the population. In clinical research, this is often referred to as the margin of error or p-value, which must be predetermined prior to calculating sample size.

There are four components of a sample size calculation; type I error (α), type II error (β), power, event rate in control group and event rate in treatment group (treatment effect) (82). Type I error is the probability of detecting a statistically significant difference when the event rates in the control and treatment groups are essentially equal. In biomedical research, type I error is commonly set at a p-value of 0.05 resulting in a 95% level of confidence. This means that the researcher is 95% confident that a type I

error will not occur. Type II error is the probability of not finding a statistically significant difference between the treatment and control group when in fact one exists. Type II error, commonly set at $\beta = 0.2$, is the most frequent type of error in clinical trials, where a statistical difference is not detected due to a limitation in the study. Power is mathematically derived from type II error represented by $(1-\beta)$. Therefore when $\beta = 0.2$ there will be an 80% chance of detecting a difference in two groups provided a difference exists. In biomedical research where there is one primary outcome, 80% power is acceptable. However, when a study design involves more than one primary outcome the level of power should be set higher (>90%) for each outcome (83).

In clinical research, sample size is often a compromise between safety, efficacy and available resources (84). Conducting an a priori sample size calculation in combination with a strong statistical design is essential for the validity and credibility of a clinical trial. The statistical design including the sample size calculation must be well outlined within the study protocol and reported with the study outcomes. Unfortunately, many trials do not report the sample size calculations in the study protocol or publications. Clinical trials with incorrect sample sizes are unethical, wasteful and potentially misleading (85). A trial with more subjects than statistically necessary may place unnecessary risk on research subjects, whereas an underpowered trial is wasteful and is at risk of a type II error. The cost of a clinical trial and the sample size are directly related, as sample size and costs increase congruently. Underpowered trials are also wasteful and do not provide statistically relevant results. Researchers must balance cost and sound statistical design for the benefit of the trial's outcome and protection of the research participants. Proper sample size calculations provide a researcher the assurance

that if a difference exists the trial's data will generate it. In one literature review, half of the RCT sample sizes studied were too small to generate appropriate effect difference and 62% failed to report a sample size calculation (86).

Missing data can negatively affect the outcome of a clinical trial by increasing the chance of a type II error when the amount of bias is similar to the anticipated treatment effect (87). Study dropouts and participants lost to follow-up are common issues due to the nature of clinical trial designs. Dropout may occur due to adverse reactions, change in eligibility or patients failing to adhere to the study requirements. Dropout potential should be factored in to both the study and statistical design. Limiting the number of follow-up appointments or decreasing the length of a study may help to keep participants enrolled (88). In addition, attrition should be part of the sample size calculation before the trial starts. Biomedical researchers need to recognize the importance of an a priori statistical calculation, especially when the results of RCTs are providing quality indicators and guiding clinical best practices.

5.2.2 Blinding

Blinding refers to the concealment of group allocation from one or more individuals involved in clinical research to eliminate expectation and subjectivity bias (89, 90). Different levels of blinding affect the design and outcomes of a study. Researchers often use the term double blind in clinical trials but fail to define the blinding process within the protocol and findings. A true double blind study requires the patient and individuals involved in the management of the patient, data collection and data analysis to be blinded to the treatment allocation.

A single blind study involves blinding only the research subject to the treatment allocation (91). Single blinded RCTs are conducted when double blinding is difficult, unethical or where objective outcomes are solely measured (for example, blood work and vital signs). Open blinded trials are most commonly conducted to compare two or more treatments, where single or double blinded methodologies are not feasible (92). Double dummy blinding is the preferred alternative when comparing two treatments (91). For example, a subject would receive two pills, one being the investigated drug and the other, placebo, blinding both the patient and the investigator to the true identity of the drug. A double blind RCT is the gold standard because it provides certainty that any significant difference between groups can be attributed to treatment effect rather than researcher or subject biases. Treatments and placebos used in a double blind study should be manufactured and packaged to look identical to maintain true double blind design. In a meta-analysis of double blind trials only 45% concealed the identification of the treatment from the control (93).

Validity refers to a tool's ability to measure what is believed the tool is measuring (94). Assessment of validity is important for peer-review processes and systematic reviews. Detection bias is an element of a study's internal validity and refers to researchers subjectivity of data collection and analysis (95). Well-executed double blind RCTs help to decrease detection bias and therefore, increase study validity. From a regulatory standpoint, validity offers credibility to a study's conclusions, which may contribute to market authorization. Randomized Control Trials without an appropriate level of blinding have larger treatment effects than double-blinded trials due to conscious or sub-conscious bias (96). Research subjects who are aware of receiving the placebo

may be less likely to comply with the study and more likely to seek treatment outside the study. Furthermore, an investigator may give less attention to the research subject receiving the placebo compared to the subject receiving the treatment. Very few studies evaluate the magnitude to which blinding was maintained and currently there is no standard method to doing so (91). Researchers need to further demonstrate and explain the blinding methods within research protocols and study publications in addition to acknowledging the importance of blinding.

5.2.3 Randomization

Randomization is the gold standard of clinical trials because it ensures that each subject has an equal chance of being assigned to any given group (80). Randomizing research subjects is important for two main reasons. First, statistical theory is built on the assumption of random sampling that represents a desired population to be studied (97). Second, randomization eliminates selection bias increasing internal validity and adding value and rigor to the research design and outcomes. By randomizing research subjects, confounding variables are balanced within the treatment and control groups, requiring less control of covariates during data analysis (98). Proper randomization requires allocation concealment where there is no a priori knowledge of the randomization design. Investigators who are privy to the randomization design may knowingly or unknowingly influence whom they do or do not recruit to the study. Ensuring allocation concealment also eliminates selection bias and improves study validity. Treatment effect was overestimated by 40% where the randomization design was unclear and treatment allocation was not preserved (99). Constructing a strong and competent randomization

framework prior to subject enrollment is essential to sound clinical research and will provide ease of data analysis.

Simple randomization is the complete random assignment of subjects into a group (100). An example is randomization by flipping a coin, heads being group A and tails being group B. Simple randomization is easy to use but only reliable in large sample sizes (>200) where equal groups are likely to be randomly generated. Block randomization is the preferred method in clinical trials because it ensures balance of sample size across groups over time (98). The number of subjects within a block should be a multiple of the number of groups. For example, if there are two groups, the block should contain four, six or eight subjects. After the researcher determines the block number, the randomization code is created by calculating and randomly arranging each sequential possibility (ie, ABAB, BABA, ABBA, BAAB). Stratified randomization controls and balances the influence of covariates by creating a separate block for each covariate (98). Subjects are then randomized within their corresponding covariate block. This randomization technique requires that all subject, be recruited prior to randomization and is therefore limited in its use due to the continuous enrollment characteristic of most clinical trials. Covariate adaptive randomization combines block and stratified techniques. Subjects are sequentially assigned to particular treatment groups considering both specific covariates and previous assignment of other subjects (98). This is useful in small sample sizes where covariates may not appropriately randomize between groups and may pose future issues with data analysis. This type of randomization technique is a valid alternative in clinical research when necessary (101).

5.3 Trial Methodology for Clinical Trial ADE002-2013

The methodologies discussed above were considered when designing Protocol Ade001-2011. The sample size was calculated using Fisher's Exact Test. Assuming 80% with no adhesions in the treatment group and 10% with no adhesions in the placebo group at six to eight weeks post surgery, 13 evaluable subjects per group are needed to demonstrate statistical difference and achieve 90% power at the 0.05 significance level. Adjusting for 10% attrition (including lost to follow-up) a total of 48 subjects will be needed in the study: 38 subjects will be recruited to the laparoscopic group (19 subjects to receive treatment, 19 subjects to receive placebo), 10 extra subjects will be recruited to undergo myomectomy by laparotomy (5 subjects to receive treatment, 5 subjects to receive placebo).

The trial will be double blind and will remain blinded until observations of the last subject is completed and all data has been collected and analyzed. The investigator, subjects, clinical coordinator and those conducting data assessment and analysis will remain blinded to the treatment allocation to reduce biased assessment of subjective outcomes. To preserve blinding of the investigated product and placebo the medication will be packaged off-site and delivered with appropriate labels to the study site. The treatment and placebo look identical and will be packaged the same, and labeled as either Group A or Group B. The trial team and subjects are blinded to the identity of Group A and Group B.

Once subjects have been deemed eligible for the study and have consented to participate, they will be randomly assigned to either Group A or Group B, each representing either the treatment group or placebo group. Randomization of treatment

assignment will increase the likelihood that any unrecognized differences between the two groups will be balanced. Block randomization will be used to assure equal sample sizes to control for variation over time and to allow for truncated recruitment if necessary. A block size of six will be used to reduce likelihood of unbalanced study groups. The randomization code was created by the study's biostatistician, Dr. Hyun-Ja Lim, and will remain in a locked cabinet in her office at the University of Saskatchewan until the end of the study and following data analysis.

CHAPTER SIX

ETHICS IN CLINICAL RESEARCH

6.1 Principles of Ethical Research

The concept of ethics in human research refers to how researchers are expected, and lawfully required, to conduct research on human subjects. A researcher has the responsibility to prioritize the protection of human rights at the fore of the scientific design and study outcome. Numerous statements, guidelines, codes, declarations and regulations have been created to address and protect human rights in medicine and research. The Principal Investigator (PI) in a clinical trial is a physician who is governed by the Hippocratic oath, a medical association's code of ethics as well as human research ethics regulations (See Section 9.2 Role of the Principal Investigator) (102). Ethical principles in medical patient care and medical research intertwine; however, it is important for a physician working in both settings to differentiate between patients and research participants (103).

Ethical considerations in research aim to protect the rights and welfare of human volunteers. Historically, research ethic codes were mandated to address unethical research where humans were mistreated. The Tuskegee Syphilis Study and the Nazi human experimentation on captive Jewish peoples by the Nazi regimes during World War II are well known historical examples of unethical research. The Tuskegee Syphilis Study was a 40-year study conducted by the United States Public Health Services that enrolled 399 African-American male sharecroppers in Alabama diagnosed with syphilis (104). In 1940 antibiotics became a known treatment for the disease but treatment was withheld from the unknowing participants in an effort to characterize end-stage syphilis.

The subject abuse displayed in the Tuskegee Syphilis Study has created distrust in medicine and research among several minority groups, specifically African Americans (105). The Nazi experiments on unwilling human subjects imprisoned against their will were grounded in Hitler's ideologies of eugenics and euthanasia (106). The Nazi doctors' research varied from studies on hypothermia to vaccinations and studies on twins. The Holocaust prisoners were abused and killed with no regard for their rights, health or well-being. Arguably, the Nazi experimentation data was collected unethically and therefore is unethical to use in current research and publications (92). The Nuremberg Code, released in 1947, was the first research code of ethics created for the United States trial against doctors involved in human experiments during World War II (107). The Nuremberg Code is a ten-point statement regulating permissible medical experimentation.

The Declaration of Helsinki, another statement of ethical principles for medical research involving human subjects, was developed by the World Medical Association (WMA) at the general assembly held in 1964 (1). The Declaration of Helsinki became the guiding backbone for the ICH-GCP guidelines and has been referenced in many ethical codes and documents (79). The declaration is also recognized by regulatory authorities and adopted by the clinical research industry to protect human volunteers participating in clinical trials. The Belmont Report was released in 1979, following the Tuskegee Syphilis study, to address unethical research conducted in the United States (108). This regulatory document is comprised of three parts: 1) boundaries between practice and research; 2) basic ethical principles; and, 3) application of these principles.

Currently, The Nuremberg Code, The Declaration of Helsinki and The Belmont Report are internationally recognized as a framework for conducting ethical human research and have guided the formation of other ethics reports. In 1991, the United States government created The Federal Policy for the Protection of Human Subjects to guide Institutional Review Boards (IRB) in reviewing and approving research protocols (109). This policy, also referred to as "the common rule", was updated in 2005 and 2009. Some argue that the "common rule" provides little guidance on how to evaluate the risk posed to human participants and the potential benefits gained by participants or society (110). In Canada, The Tri-Council Policy Statement (TCPS) for ethical conduct of research involving humans is the guidance document for sponsors, Research Ethics Boards (REB), investigators and other research personnel (4). The first edition of the TCPS was created in 1998 and replaced by the second edition TCPS in 2010. The second edition contains updated guidelines for clinical trials, changes to select research terminology and consolidation of core principles (111). The protection and consideration of humans in clinical research have vastly improved over the past 75 years due to new policies and regulations. The protection of human rights and welfare has become the over arching obligation in clinical research and therefore influencing study design and conduct of regulations and expectations that exist within the research community. It is the responsibility and priority of researchers to consider and protect the study participants above all other study responsibilities.

The three guiding ethical principles in clinical research, as articulated by the Belmont Report, are respect for persons, beneficence and justice. The concept of respect for persons addresses the need for all humans to be treated as equal sentient individuals

who must not be solely viewed as research participants. Individuals have a right to choose to volunteer for a study and to discontinue participation at any point without penalty or mistreatment. An individuals' right to volunteer absolutely requires that the individual is well informed of study rationale, procedures, risks and potential benefits and has been an active party in the consenting process, with questions or concerns answered. In no circumstance should research participants be led to believe they are receiving an efficacious treatment. Approved drugs currently used in the investigated product's indication should be used as the control where available. Where there is no standard of care available, a placebo may be used. In placebo-controlled studies, research participants must understand that they may not receive any treatment at all. It is also important to understand that a placebo should only be used where there is no standard of care and should never be used where there is a risk for deterioration of the disease (112, 113).

Respect for persons also requires the protection of vulnerable peoples termed "immature or incapacitated" by the Principle Investigator (108). Where vulnerable peoples lack the ability to make sound decisions for themselves, assent must be obtained by the vulnerable person and consent obtained by a legal guardian who is charged with acting in the vulnerable person's best interest.

Beneficence requires the researcher and the research design to maximize the benefit of the potential study outcomes while concurrently minimizing any possible harm to the study participant. This principle sparks the argument of unnecessary clinical research with little or no useful outcome. Studies must address patient needs and gaps in medical knowledge. Endpoints should focus on a medical problem with the potential to

contribute to future medical treatments and expertise. Researchers should avoid duplicating research to decrease the number of participants exposed to potential risks of a study. Research ethics and scientifically sound research are intuitively intertwined. Therefore, poorly designed research exposes participants to risk with no benefit (114). Research must have value and be valid to meet ethical expectations. Validity implies sound scientific design and the concept of value requires strong potential outcomes of more than a trivial nature (115). For example, a clinical trial may be appropriately powered with the statistically correct number of participants, participants randomized and researchers blinded to treatment and control groups to decrease bias; however if the hypothesis does not address a healthcare need and aim to improve patient outcomes, the trial does not have value and is therefore not ethical. It would also be unethical to conduct a trial addressing a medical need but lacking sound study design (validity).

The principle of justice builds on beneficence to distribute the benefits and risk of research fairly. Justice in research implies that those who are exposed to the risk of research should also be benefited (79). It is important to examine the selection of research participants to ensure that specific groups of people are not being recruited because they are easily accessed or manipulated. This may include low socioeconomic groups, racial minorities, mentally disabled or persons confined to an institution. Vulnerable groups such as these are to be protected against exploitation of research as historically demonstrated by experiments such as the Tuskegee Syphilis Study (116). Where applicable, researchers must ensure representation from different gender, age, race and socioeconomic groups.

6.2 Canadian Research Ethics Board (REB)

Principle investigators and other researchers must obtain ethical approval from a REB prior to the start of any studies involving human subjects. The responsibility of a REB is to review, grant ethical approval and monitor the research ongoing within its jurisdiction. Many universities and research institutes have their own governing REB, which is responsible for reviewing and approving all research involving humans conducted within the institution. Smaller institutes may function under another institution's REB or submit to an independent central REB. Canadian REB are expected to function according to the TCPS2 policies and guidelines, specifically Chapter 6: Governance of Research Ethics Review (4). REB committees must be comprised of at least five members and include both men and women. At least two of the members must have expertise in the relevant areas of research. One member must have knowledge in ethics. One member must have relevant law expertise but must not be providing the institution with legal council. One member must be from the local community with no affiliation to the institution. A recent Curriculum Vitae (CV) of each member of the committee should be kept on file at the REB office to demonstrate and document the expertise of each committee member. All committee members must be physically present for a REB meeting. In case of an absence, it is recommended that there be substitute committee members available to fulfill the member requirements. To protect and ensure the integrity of the REB committee and its decisions, a committee member must not participate in the review of any submission in which they may have a real, or perceived, conflict of interest

Approval of a clinical research study by an REB applies to the ethical acceptability of a clinical trial protocol but does not constitute as authorization for the execution of the protocol. Clinical trials for pharmaceutics, devices and biologics require both REB and Health Canada approval prior to enrolling subjects. A REB may consult applicable experts to review and guide the decision making process where committee members lack expertise in the submission's area of study. For example, a REB may choose to consult an oncologist for a study protocol investigating a novel chemotherapy.

Research Ethics Board submissions require a formal research proposal written to the committee members. Any study documents related to ethical conduct or involving the research participant must be submitted with the proposal. This includes, but is not limited to: the research protocol, an investigator's brochure (IB), a consent form, information pamphlets for research participants, diary cards, surveys and any methods to be used for participant recruitment (See Section 7.2 Clinical Trial Application Document Requirements). Research Ethics Board submissions also require approval or rejection documents from other REB or Health Canada. Once a study is approved, the PI must comply with communication stipulations set by Health Canada and REB to maintain high ethical standards. Communications include annual renewals, document amendments, adverse events and study closures which need to be promptly reported to the REB and Health Canada.

6.3 Ethics Approval Process for the Clinical Trial ADE002-2013

My role in the ethics submission and approval process was expanded from the traditional role of the clinical coordinator. I worked closely with the PI and research team to develop the biological/medical hypothesis to be tested. As a result of my

involvement in the clinical sciences aspects of the CT, I proceeded to develop the research proposal and ethics application on behalf of the PI. The PI and I subsequently drafted all versions of the proposal, communications with Health Canada and University of Saskatchewan and Saskatoon Regional Health District approval processes. The application was organized and the documents were completed. The ethics application was submitted in a timely manner to the appropriate personnel for the May 2011 Biomedical Research Ethics Board meeting as outlined in the foregoing. April of 2011, a research proposal for the clinical trial protocol ADE001-2011 and all required study documents were submitted to the University of Saskatchewan Biomedical Research Ethics Board for ethical review and approval of Protocol ADE001-2011. Study documents for this submission included the research protocol (Appendix A), IB (Appendix E), consent form (Appendix D) and diary card (Appendix F).

On May 30, 2011, following the first review, the REB chair required clarification and amendments to the consent form and research proposal. Clarifications included specifying who was responsible for the consent process, and storage and monitoring of investigational product. The REB also required further information related to rationale of the study, pathophysiology of adhesions, existing safety data and indicated use of the investigated product. The REB requested the consent form to be written in simple language and to clearly specify emergency contacts. The PI is responsible for the REB submission, amendment and all other communications between the REB and trial site. In the expanded role of the clinical coordinator, I was able to submit, amend and communicate with the REB on behalf of the PI. Together, Dr. Chizen and myself amended the research proposal and consent form and resubmitted to the REB in June

2011. On July 6, 2011, the trial received ethics approval filed under BIO# 11-92. Ethics approval was renewed in July 2012. In July 2013 the protocol was amended and renamed ADE002-2013 [Appendix A]. Laparoscopic salpingostomy was changed to laparoscopic and laparotomy myomectomy. Myomectomy is well known for postoperative adhesion formation and was; therefore, chosen as an improved model for adhesion assessment at the time of second look laparoscopy. Salpignostomy to remove an ectopic pregnancy is an urgent or emergency surgery, making subject recruitment and enrollment difficult. The change in gynecological surgery may also help with subject recruitment and enrollment. The laparotomy group was added to observe adhesion development in both types of surgery. I discussed the protocol amendments with the PI and Biomedical Research Ethics Chair and ethics approval for the trial was renewed in July 2013.

Figure 1 Timeline outlining the Biomedical Research Ethics Board submissions, amendments, approval and renewals at the University of Saskatchewan for Protocol ADE001 and ADE002.

CHAPTER SEVEN

CANADIAN REGULATORY AUTHORITY

7.1 Health Canada

Health Canada is the federal department of the Government of Canada responsible for maintaining and improving the health of Canadians. Health Canada's mission is to make Canada one of the healthiest countries while respecting individual choices and individual circumstances. Health Canada is made up of many departments and agencies that address different categories and issues of the broader concepts of health. The Therapeutic Products Directorate (TPD) is the Canadian federal authority that regulates pharmaceutical drugs and medical devices designed for human use (117). The authority and actions of the TPD are regulated by the Food and Drugs Act, Part C, Section 5 for all clinical research in Canada (118). In addition, Health Canada is one of the nine members of the ICH Steering Committee; therefore, the TPD adheres to the ICH/GCP guidelines [Appendix B].

Prior to the initiation of a clinical trial in Canada, sponsors or PIs must submit a Clinical Trial Application (CTA) to the TPD (See Section 9.1 Role of the Sponsor and Section 9.2 Role of the Principal Investigator). Health Canada must assign each CTA with an individual control number, review the CTA and notify the sponsor within 30 days of the filing date if the application is found to be deficient (119). Deficiencies may include incomplete or missing documents, vague study background and rationale, and ethical concerns. A deficient CTA may be addressed with a request for clarification or a screening rejection letter. A request for clarification requires the sponsor or PI to address the concerns within two calendar days. Failure to reply to a request for clarification will

result in a screening rejection letter, which outlines the deficiencies of the application. If a CTA is rejected, resubmission of the CTA will then be processed as a new application and assigned a new control number. If the request for clarification is addressed and/or CTA is without deficiency, Health Canada will issue a No Objection Letter (NOL) to the sponsor. The sponsor is then responsible for notifying Health Canada of the study start date. Other notifications, such as study document amendments; serious adverse events and study closure remain the responsibility of the sponsor.

In Spring/Summer of 2008, Health Canada consulted with stakeholders representing industry, government, academia, and non-government organizations to address issues and restructure the CTA process. The group aimed to provide a framework for the TPD for efficient review of CTA submissions and create guidance documents to help industry meet regulatory obligations (120). The document entitled *"Guidance for Clinical Trial Sponsors"*, outlines step-by-step instructions for organizing, developing and submitting a complete CTA (119). Compliance with this document is expected to decrease CTA deficiencies and expedite Health Canada's review and approval process. Sponsors, PIs and other research personnel should read and frequently reference both documents prior to submitting a CTA and conducting clinical trials in Canada. Failure to follow procedures and provide timely information can result in fines, termination of the trial, and/or imprisonment should the failure be attributed to negligent and malicious acts. In the case of investigator-initiated trials, the PI assumes the roles and responsibilities of the sponsor and should adhere to the Health Canada guidance documents with this understanding. Most commonly, investigators functioning within an academic setting will seek out government and other public funding or grants for their

clinical trials. Investigators may also choose to obtain financial funding from a pharmaceutical sponsor. In this situation, the PI should consult Health Canada to clarify the language surrounding the investigator-initiated trial versus industry-sponsored trial. The language is extremely important so that all stakeholders involved are aware of who is responsible for what.

7.2 Clinical Trial Application Document Requirements

A CTA is comprised of three modules that must each be completed in accordance with Health Canada requirements and submitted in separate binders. Module One contains administrative clinical information, which includes a Protocol Synopsis (PSEAT-CTA), Protocol, Consent Form, IB and a Drug Submission Application Form (HC/SC 3011). Module Two contains the common technical document summaries, which includes the quality (chemistry and manufacturing) information for the investigated drug. Quality Overall Summary requirements differ for each phase of research and therefore cannot be cross-referenced throughout drug development stages. The different requirements and Quality Overall Summary templates for each stage of drug development are provided in the *Guidance to Clinical Trial Sponsors* document (119). Module Three is only necessary for reporting any additional supporting quality information that was not required in Module Two. Additional information provided by the sponsor in Module Three must be appropriately cross-referenced to the corresponding data in Module Two.

7.2.1 Protocol Development

A clinical trial protocol is a document that thoroughly describes the objectives, design, methodology, statistical design and analyses and organization of a clinical trial

(121). Traditionally, in industry-sponsored clinical trials, the sponsor develops the protocol, assigns a unique identification number and provides the protocol to each study site as a manual for conducting the clinical trial. In investigator-initiated clinical trials the PI assumes all the sponsor's responsibilities including protocol development, identification number assignment and trial site setup. Study protocols vary in format; however, there are key elements that must be included. Section 6 of the ICH/GCP E6 guidelines provides an outline of essential topics to be included in a clinical research protocol (3). A protocol should begin with a rationale for the study, provide a background of the science behind the rationale and the benefit of potential study outcomes. The objectives and endpoints must also be outlined. A clinical trial endpoint is defined as a measure that allows the researcher to decide to reject or accept the null hypothesis (122). A primary endpoint will answer the primary question of the clinical trial, which is most often efficacy of the investigated product. A secondary endpoint will address other relevant questions, for example, safety data or adverse events. Next, non-clinical and clinical studies that have been conducted on or in relation to the investigational product including safety and quality should be summarized in a review of the relevant literature with appropriate references. A section explaining the rationale for route of administration and dose(s) to be administered according to the protocol should follow.

The study designs must provide a detailed description of the study procedures and function as instructions for the study site. The design must clearly outline how exactly the study will be conducted and should include the number of participants required for enrollment, inclusion and exclusion criteria for the study, blinding processes,

randomization and intervention allocation based upon the study's statistical power calculations (Refer to Section 5.2 Research Design). The inclusion and exclusion criteria are measures and requirements of a research participant to determine study eligibility. A section discussing treatment plan and study assessments will follow. This section should include any physical assessments to be performed by the PI or designate, required blood work and who is responsible for phlebotomy, how and by whom, the drug will be dosed and administered and follow up assessments, visits or phone calls. A flowchart with the sequence of the trial and a schedule of events in table format should be provided to support the study design.

The statistics section should describe the sample size calculation and variables used, any interim analyses planned, procedures for handling potential missing data, and the final statistical design for analysis of data collected and assumptions underlying the statistical analyses. Adverse events and severe adverse events (SAE) should be defined and methods for reporting should be described. Data handling and record keeping should also be described. At present Health Canada requires that any documents or data related to the clinical trial must be stored in a locked facility for 25 years (119). The study monitor must conduct a final visit prior to the study closure. The monitor ensures and documents that all activities required for study closeout are complete and copies of essential documents are filed appropriately in the Trial Master File (See section 8.3.3 Trial Master File). The sponsor must report study closure to Health Canada, the PI and to the REB. The sponsor and/or PI will create a clinical study report to document results and interpretations of the trial. A copy of the clinical study report must be sent to Health

Canada with the study closure notification. The PI may provide the REB with a copy of the report where required.

7.2.2 Investigator's Brochure

An Investigator's Brochure (IB) contains information about the investigational product in an objective and non-promotional manner. The IB requirements are outlined in Section 7 of the ICH/GCP E6 guidelines (3). The document must contain nonclinical and clinical data as well as safety and toxicity data related to the investigational product with appropriate references to support the rationale for the trial. Non-clinical trials conducted on the investigated product prior to consideration of human trials must be described. Physical, chemical and pharmaceutical properties and formulations are provided, including the molecular structure and formula, and characteristics of the active ingredient(s). The sponsor is responsible for updating the IB as new research or information on or related to the investigated product becomes available. The market experience of an investigated product that is currently approved and commercially available for an indication outside of the clinical trial must be described. This should include the drug company, countries in which the product is sold, date of regulatory market authorization and sales statistics. The last section of the IB is termed *Summary of Data and Guidance for the Investigator*. This section should provide the investigator with a summary of the above data as well as any expected or potential adverse reactions, overdose and toxicity information noted from previous human experience or pharmacology of the drug. Information presented in this section should describe background information on the investigated product and outline study endpoints to concisely support the rationale for conducting the clinical trial.

Overall, the IB aims to educate the investigator on the scientific and pharmacologic background of the drug, allowing him/her to balance risks and benefits for patients that may be recruited/included in the study without bias. The adequacy of the IB will be determined by Health Canada in accordance to the ICH/GCP guidelines.

7.2.3 The Consent Form

The process for obtaining consent from individuals who may be appropriate to include in the study is outlined in Section 4.8 of the ICH/GCP E6 Guidelines (3). Obtaining informed consent is one of the most critiqued processes of clinical research (116). A signed consent form implies that the research subject is making a fully informed decision to voluntarily participate in the clinical trial (123). In order for the subject to be fully informed they must understand the methodology of the research and any risks and benefits of their participation. Often participants fail to understand the objectives and scientific design of clinical studies. Many participants believe that the investigated product and their involvement in the study will benefit them directly; this is known as the therapeutic misconception (124). To avoid this misconception, potential participants need to understand the scientific methodology, such as blinding, randomization and the potential of receiving a placebo, and translate that understanding into how the study will or will not affect them directly. Unfortunately, many study participants are unable to differentiate between research and treatment and therefore are not truly informed (125). Educating the potential participant is the ongoing responsibility of the PI or their designate involved in the consenting process throughout the clinical trial.

The process of obtaining consent begins when the potential participant is first informed about the study and ends when the participant has completed the study

requirements or is lost to follow up. The consenting process is two-fold; the process consists of the consent form itself and how the information in the consent form is explained. Regulatory authorities and REB provide guidelines for developing an appropriate consent form [See Appendix C]. Scientific or medical words should be explained using simple terminology. Most REB require consent forms at a Grade 8 reading comprehension level. To avoid statements with false information the term "I understand" should not be used. The use of voluntary language is essential and participants must understand that it is their autonomous decision to participate, refuse or withdraw at any time during the trial. Coercive language should be avoided in the text and during the consenting process. The consenter must clearly state and explain any risks of participations without making claims of definite benefit from participating in the clinical trial. The consent form must describe how the researchers plan to protect the anonymity of the potential participant and information collected. Literacy, education, socio-economic status and language are common barriers to the consenting process. Consent forms need to meet the needs of the population being studied in order to address these barriers (126). Each study site should modify the consent form to eliminate potential barriers and target site populations. The REB will deem the consent form as appropriate and adequate for the study site. The ethical principle of respect for persons requires that the consenting process foster an environment of informed and voluntary decisions free of manipulation and coercion. The ethical principle of justice protects vulnerable groups against targeted recruitment as well as under representation in research.

7.3 Clinical Trial Application Process for Clinical Trial ADE002-2013

The current clinical trial ADE002-2013 is an investigator-initiated study; therefore, the PI and her research team developed the documents required for the Health Canada CTA. In creating a new model for the clinical coordinator with an expanded role in an investigator-initiated clinical trial, I was responsible for developing the required documentation for the Health Canada Clinical Trial Application. Protocol development began in June 2010 by Dr. Donna Chizen, PI, Dr. Roger Pierson, sub-investigator and myself as the clinical coordinator. A biostatistician, Dr. Hyun-Ja Lim, at the University of Saskatchewan created the statistical design and data analysis contracts. I also developed the Consent Form [Appendix D], Investigator's Brochure [Appendix E] and Diary Card [Appendix F] attached as appendices to the protocol. I worked closely with the PI to develop the final formats of each document.

I submitted the CTA for Protocol Ade001-2011 to Health Canada on August 11, 2011on behalf of the PI and research team. Only Modules One and Two were necessary for the Phase II application, both organized into individual binders. A CD-ROM with required electronic documents was included in the CTA package. A notice for clarification and screening rejection letter were not received within 30 days of submission. A NOL was received on October 24, 2011 and was filed with the University of Saskatchewan Biomedical Ethics Board under Bio# 11-92. In March 2012, the investigated products temperature storage requirements changed from room temperature to between two to eight degrees Celsius. In August 2012, the adhesion grading process changed from the surgeon's responsibility to a central visual evaluation with 3 independent assessors. In May 2013, the trial surgery changed from laparoscopic

salpingostomy to myomectomy performed at laparoscopy or at laparotomy. The most recent protocol is Protocol ADE002-2013 [Appendix A]. On all three occasions, I amended the protocol to reflect the changes and Health Canada was immediately notified via facsimile. Health Canada acknowledged the notifications via return facsimile. All regulatory documents are kept in a locked trial cabinet and an electronic Trial Master File (TMF) as required by ICH/GCP guidelines.

Developing all the necessary documentation as well as compiling, organizing and submitting the Health Canada CTA greatly contributed to my experiential learning as a clinical coordinator. My education and experience as a RN provided a foundation from which I was able to develop all of the clinical trial documentation. General medical knowledge and the ability to seek resources for information and support are strengths that a RN brings to the expanded role of the clinical coordinator. Attention to detail, organization and autonomy are also strengths of the RN that assisted in application preparation and submission. I consulted the Health Canada guidance documents as well as the expertise of the members of the clinical research team. From this experience, I am prepared to develop new protocols and other supplemental documents required for a clinical trial. I am also able to successfully compile and submit Health Canada CTA applications for the approval of a human clinical trial in Canada.

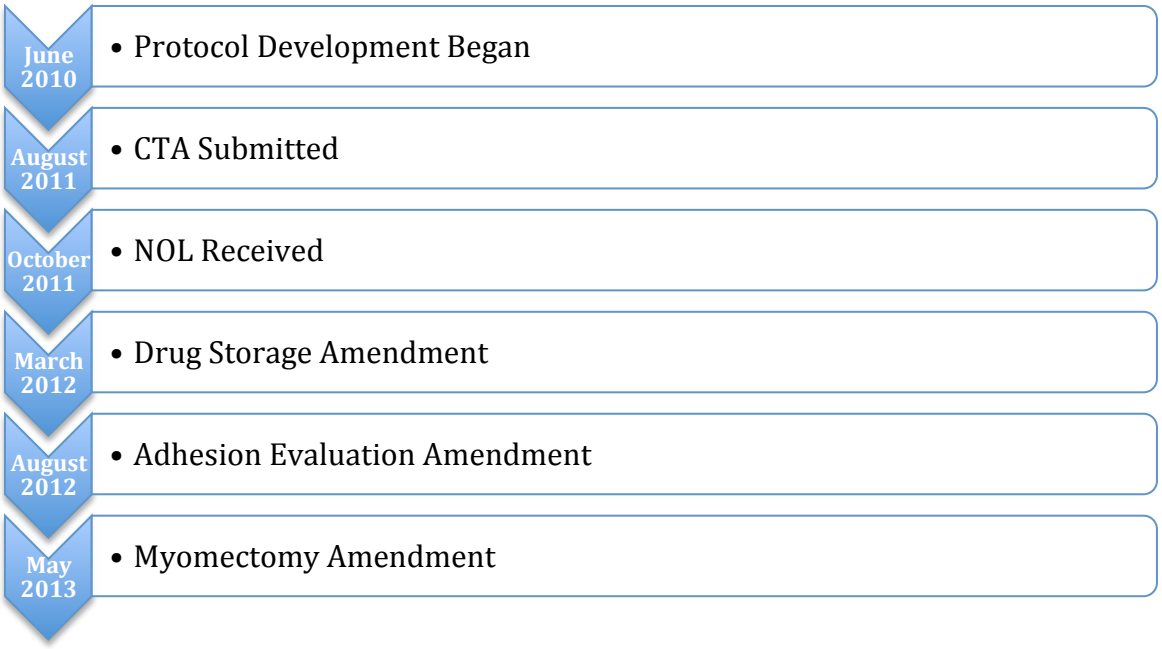

Figure 2 This timeline outlines the Health Canada Clinical Trial Application process for Protocol ADE001 and ADE002.

CHAPTER EIGHT

CONDUCTING A CLINICAL TRIAL

8.1 Good Clinical Practice

The International Conference on Harmonization (ICH) of technical requirements for the registration of pharmaceutics for humans aims to provide ethical and scientific quality standards for design, conduct, data collection and reporting in clinical trials around the world. The ten members of the ICH Steering Committee determine policies and procedures, select topics for harmonization and monitor the progress of their initiatives. Members of the ICH Steering Committee include but are not limited to Health Canada, the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), World Health Organization (WHO) and Japan Pharmaceutical Manufacturers Association (JPMA).

There are four main categories of ICH guidelines. Each has an expert working group. The groups are: quality, safety, efficacy and multidisciplinary. In 1996, the Efficacy Expert Working Group developed the Good Clinical Practice (GCP) guidelines (E6). The two main goals of the ICH/GCP E6 guidelines are: 1) to assure the public that rights, safety and well-being of subjects are protected according to the Declaration of Helsinki; and 2) to ensure that clinical data obtained in a ICH/GCP compliant clinical trial will meet regulatory requirements. In 1997, the European Union, United States and Japan adopted the ICH/GCP guidelines for clinical research within their countries. Since then, the WHO and Health Canada have also acknowledged the ICH/GCP E6 guidelines (2). Guidelines provide a standard to advise practice without carrying any legal implications or expectations. As guidelines become adopted and part of the practiced

norm they are integrated into national regulations (79). ICH guidelines were created to harmonize and lead clinical research in different countries without being an official statute, but have since been referenced in national regulations and policies. Canadian regulations are consistent with principles of ICH/ GCP E6: Consolidated Guidelines, E8: General Considerations of Clinical Trials, and E2A: Clinical Safety Data Management (3). Japan, the European Union, Unites States and WHO have also created regulations and policies consistent with ICH guidelines for conducting clinical trials. The number of clinical trials and ICH/GCP compliant trial sites in developing countries have increased over the last ten years (127). As clinical research presence continues to increase, ICH/GCP guidelines may become a basis for research regulations in developing countries (128).

Good Clinical Practice guidelines are considered the international gold standard for clinical research conduct and they are integrated into national policy and regulations; however, some researchers question their value. Some criticize the title Good Clinical Practice claiming it sounds like guidelines for patient care rather than research (129). Best practices influence patient care yet clinical research guidelines are merely labeled as "good". The ICH/GCP guidelines have been labeled as ethically weak when compared to other documents such as the Belmont Report and Declaration of Helsinki (130). Categorizing GCP guidelines under efficacy rather than safety leads some to believe that the ICH priority is drug development before the protection of human subjects. Others are concerned with the amount of responsibility GCP guidelines place on the REB, specifically in emerging markets where REB are often inexperienced with limited resources (129, 131). Researchers argue that GCP guidelines fail to focus on scientific

validity and weigh heavily on administrative tasks (132). Increasing costs and regulatory pressure may discourage investigator-initiated clinical trials (133). Good Clinical Procedures guidelines have not been updated since inception and may need to be amended to address the rising costs and scientific concerns. The ICH steering committee should include representation from more countries, especially emerging markets experiencing clinical trial growth. The shift in clinical trials from the United States and European Union to complete clinical trials in other countries may provide an incentive for change.

8.2 Standard Operating Procedures

Standard Operating Procedures (SOP) are detailed written instructions to achieve uniformity of the performance of a specific function (3). In clinical research, SOP ensure regulatory compliance and safe work practice by minimizing ambiguity at the trial site or by the sponsor. Sponsors, research sites, REB, Health Canada and any other research agencies must have SOP that guide each of their internal processes. SOP should be specifically written or adapted for the trial site. Standard Operating Procedures become the foundation for training members of the research team. Research personnel should be trained on and notified of amendments of each SOP applicable to their job. Training logs should be kept and maintained for each person (134). Proper SOP implementation protects research subjects by assuring quality and consistency in every aspect of the clinical trial.

Developing and implementing research site SOP is a time consuming task; however, clear SOP are critical to the trial setup and conduct. The document development begins by composing a SOP template with numerical headings and

identifying the SOP required for each clinical trial domain. For example, there must be individual SOP for the consent process, communication with Health Canada and the REB, data storage and drug monitoring. Elements of an SOP include a title, definitions, scope, a list of procedures, signatures and history of creation, implementation and amendment. The SOP begins with a title identifying the activity outlined below. Next, the purpose of the SOP is explained in short, concise language with associated guidelines, regulations or policies listed as references. Complex words and abbreviations used throughout the SOP must be defined. The scope of the SOP identifies whom the SOP applies to and outlines the expectations and responsibilities. The procedure list should be written in short, point-form sentences to outline the sequence of events that are expected to occur. Appropriate signatures and dates denote authorization of each of the SOP. A history of the SOP development, implementation and amendments may be listed at the beginning or end of the SOP. Strong SOP are written with clear and concise language cross-referencing other SOP to support practice. Standard Operating Procedure deviations include any activities that oppose the list of procedures. Deviations should be documented and addressed with a Corrective Action Preventive Action (CAPA) plan if necessary. Multiple deviations may be due to an SOP that is too detailed, unattainable or does not reflect current practice. Sponsors and research sites should be cognizant of repeated deviations and address the deviations respectively. Standard operating procedures should undergo evaluation, be routinely updated and appropriately documented at regular intervals determined by protocol amendments, deviations, and adverse events (135).

8.3 Clinical Trial Setup

8.3.1 Laboratory

Most clinical trials involve laboratory tests to monitor safety and/or treatment effects of the investigational product. A central or community laboratory may be used depending on the research site's resources and the agreement between the site and sponsor. All laboratories providing analyses and data for the clinical trial must function in accordance with Good Laboratory Practice (GLP), be accredited and have up-to-date certifications. In Canada, laboratory accreditation is regulated through the Standard Counsel of Canada mandated by the *Standard Council of Canada Act* (136). The sponsor and the research site must file copies of the current accreditation and certification records. The site and sponsor must also retain normal values and ranges of the laboratory tests involved in the protocol. Routine equipment quality control testing must be performed to ensure the laboratory results obtained are accurate. The sponsor and/or the site should conduct and document a laboratory visit prior to the trial commencement. Laboratory results are source documents and must be handled accordingly (See Section 8.3.5 Source Documents).

8.3.2 Handling the Investigational Product

The sponsor is responsible for manufacturing, labeling and shipping the investigational product according to the study protocol and ICH/GCP guidelines. The study site must have all appropriate documents, equipment and drug handling training in place before receiving the drug from the sponsor. For example, this may include a locked facility, a refrigerator, temperature monitoring equipment and staff trained on the corresponding SOP. Sample drug labels should be kept in the TMF (Refer to Section

8.3.3 Trial Master File). The sponsor must maintain shipping records for the investigational product including batch numbers and shipping conditions. Shipping conditions must specify if the drug was transported at room temperature or a cold chain monitored by the shipping company. Once the drug is received, the site is responsible for maintaining a locked storage area and monitoring the drug according to the protocol. For investigational products that require specific temperature storage, temperature logs must be kept according to the sponsor and/or site SOP for drug monitoring. The site must use drug accountability logs to monitor drugs received from sponsor, dispensed to research participants and shipped back to the sponsor. The drug accountability log should include dates, times, batch number, and participant identification if applicable. Study sites may utilize a hospital pharmacy appropriately licensed or designated to store, monitor and/or dispense the investigational product. The site and sponsor must have appropriate pharmacy accreditation and certification documents.

8.3.3 Trial Master File

The Trial Master File contains the essential documents needed to set up, conduct and close a clinical trial. Essential documents are defined by the ICH/GCP guidelines as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced (3). The TMF should be established at the beginning of a clinical trial and be maintained by the sponsor and each research site. The TMF is to be updated as documents are amended throughout the trial. Internal monitors employed by the sponsor and audits conducted by regulatory authorities will request access to the TMF to assess the trial's quality and compliance with regulations and guidelines. TMF kept in paper format must be kept in a secure location accessible by

relevant study site staff. The TMF may be kept on an electronic database for clinical trials using electronic data management systems. The database must comply with ICH/GCP guidelines and regulatory standards for data storage and handling.

8.3.4 Case Report Forms

A research participant's individual Case Report Form (CRF) is similar in concept to a patient's medical chart. The CRF contains data gathered solely for the purpose of the study and includes but is not limited to signed consent forms, medical history, laboratory results, drug administration and adverse events. The CRF is designed in accordance with the study protocol and may require amendments if the protocol is amended. Maintaining organized and completed CRF are essential to trial quality and improve audit outcomes. An internal monitor is employed or contracted by the sponsor and is responsible for ensuring the study site is complying with the study protocol, GCP guidelines and regulatory requirements. An internal monitor will review the CRF and have access to patient charts to verify collected data at regular intervals throughout the trial (135). A well-organized CRF should lead an auditor through a participant's involvement beginning with screening, inclusion/exclusion criteria and consent to follow-up appointments and study closure.

8.3.5 Source Documents

Source documents are the original documents or records related to the research participant generated before, during and after the completion or termination of a clinical trial (137). Most source data are collected from the participant, medical record or laboratory (138). Source data includes, but is not limited to, hospital and medical office charts, laboratory reports, x-rays, diary card, and drug dispensing records. Source

documents must enable the reconstruction and evaluation of a trial, allowing a third-party to verify and reconfirm the trial's data (139).

Inaccurate or inadequate case report forms and source documents were the second most common deficiency during United States FDA site inspections and fifth top deficiency reported by the European Medicines Agency (EMA) (139). The FDA developed the ALCOA principle to guide and improve source documentation (137). Data must be attributable, legible, contemporaneous, original and accurate. Attributable implies that the identity of who recorded the data must be clear and legibility implies neatness and readability. Attributable and legible data has been improved by electronic documentation. Contemporaneous requires the data to be recorded and referenced to in the correct time frame. For example, the date of consent should precede trial related tests and treatments. Late entries must be identified and explained. Original data should be attainable to verify data collected and recorded. Patient medical records must be available for monitors or regulatory auditors. Copies stored in the participant's file must be an exact copy of the original. Data must be accurate, which requires attentive data recording and entry. For example, in clinical trials involving surgical procedures, post-operative vital signs found in the patient's chart (source document) should be identical to those recorded in the CRF. Appropriate courses and training for sponsors and site research staff will improve the quality of documentation and data capture (140). Every research site should have an SOP for creating and handling source documentation.

A discrepancy in clinical research and data monitoring is defined as a data point that fails to pass a validation check. A discrepancy may be due to data that do not fall within an appropriate range, missing data and protocol deviations (141). In addition to

these discrepancies, it is imperative that all CRF data be consistent with source documentation. Any outstanding variations or changes to the CRF must be appropriately addressed and explained, if applicable. Study sites should have an SOP for making changes and correcting errors in source documents (142). The data points should be individually defined to decrease variation in understanding between staff and across sites (143). For example, one study site may classify obese as a Body Mass Index (BMI) greater than 30 while another site uses greater than 35. A collaborative understanding will help to decrease discrepancies and increase validity of the data.

Over the past decade, clinical research has become more reliant on digital technologies for handling and storing data. Electronic Data Capturing (EDC) may help to decrease many common faults of source documentation. Frequently data are first recorded on paper (source document) and later entered into a digital database. This sequence of events creates a greater chance for translational error. New technologies allow sites to capture data immediately into the CRF via personal computers or tablets. Electronic CRF can also decrease time and increase efficiency in other areas of a trial. Prompts for missing or erroneous data provide ease of use for the coordinator, quality data input for the sponsor and decreased audit time for the internal or external monitors. Electronic CRF are also effective when extracting and organizing data for interim or end of study analysis. The Society of Clinical Data Management (SCDM) created Good Clinical Data Management guidelines to help sponsors effectively collect and manage electronic data while complying with ICH/GCP guidelines and FDA regulations (141).

8.4 Current Clinical Trial Setup

Our study site in the Department of Obstetrics, Gynecology & Reproductive Sciences at the University of Saskatchewan (Saskatoon, SK) adopted the Network of Networks (N2) SOP for conducting clinical research. Network of Networks aim to enable and enhance clinical research capabilities and capacity in Canada by providing members with references and tools to facilitate clinical research. The University of Saskatchewan is a member of N2, and therefore, has access to the available tools, including SOP. The PI, Dr. Donna Chizen and myself, the clinical coordinator, developed a laparoscopy and laparotomy myomectomy SOP outlining basic processes for each surgery [Appendix G]. As the clinical coordinator I was responsible for maintaining the SOPs applicable to our trial site.

The clinical coordinator monitors the refrigerator's temperature where the investigated product is stored and records the temperature in the temperature logbook. The investigational drug for the clinical trial ADE002-2013 was received at the University of Saskatchewan, Department of Obstetrics and Gynecology & Reproductive Sciences (Saskatoon, SK) in August 2012 via an undisturbed cold chain supply from Dalton Pharma Services (Toronto, ON). A cold chain supply is a temperature-controlled storage and distribution processes. I was also responsible for maintaining shipment records and recording inventory and lot numbers. A refrigeration failure was detected on August 2, 2013 with a temperature of 20.3 degrees Celsius. Drugs were immediately transported offsite in a temperature-monitored refrigerator. I developed a CAPA plan and filed it in the TMF. A sample of the investigated product was sent back to Dalton Pharma Services via a cold chain supply to test for instability and growth. The number of

vials in the tested sample (32) was calculated by taking the square root of the original number of vials (963) manufactured. Samples were confirmed to be stable with no impurities.

Clinical trial site setup must follow ICH/GCP guidelines, requires organization, and detailed record maintenance. The setup of a trial can directly effect the execution of a trial and therefore, the data obtained. My experience in the new role of an enhanced clinical coordinator taught me how to appropriately setup a clinical trial in compliance with the ICH/GCP guidelines and regulatory expectations. From this experience, I can setup trial sites for the execution of approved clinical trials and mentor other clinical coordinators.

CHAPTER NINE

ROLES AND RESPONSIBLIITES OF THE CLINICAL RESEARCH TEAM AND THE REGISTERED NURSE AS A CLINICAL RESEARCH PROFESSIONAL

9.1 Role of the Sponsor

The sponsor is typically defined as the pharmaceutical company responsible for the research and development of an investigational product (drug or medical device) in an industry-initiated clinical trial. The sponsor's role and responsibility in a clinical trial is outlined in Section 5.0 of the ICH/GCP guidelines. The sponsor develops the study protocol and other documentation such as the IB and consent forms. The sponsor is responsible for manufacture, packaging, labeling and coding the investigational product. Once study documents are finalized and the product is manufactured, packaged and labeled, the sponsor must submit a CTA to Health Canada to obtain regulatory approval. Following the receipt of an NOL from Health Canada, the sponsor will negotiate and sign clinical trial agreements with the PI at trial site(s). The sponsor is responsible for keeping records of the clinical trial agreement in the TMF. The sponsor is also responsible for training the PI and clinical coordinator on the study protocol. The PI must be aware of any changes to the protocol or updates to the IB. The sponsor must designate appropriate investigators at acceptable research sites determined by a pre-study visit. A pre-study visit will also indicate the adequacy of the site, training and experience of the study staff and relevance of the patient population to the study's enrollment criteria.

Once a trial has started and participants have been enrolled, quality assurance and control becomes the sponsor's primary responsibility. The sponsor must have Standard Operating Procedures (SOP) for trial execution, data generation, recording and reporting

in compliance with the clinical trial protocol, ICH/GCP guidelines and Health Canada's regulations (See Section 8.2 Standard Operating Procedures). The sponsor will designate clinical monitor(s) to conduct regular site visits to verify that the conduct of the trial is in compliance with the SOPs, reported trial data are accurate, complete and verifiable against source data and the rights and well-being of human subjects enrolled are protected. Selection of appropriate monitors and provision of adequate training are critical for quality monitoring outcomes. The sponsor must appropriately and punctually handle non-compliance issues found by a site monitor. The sponsor is also responsible for reporting adverse drug effects to regulatory authorities and other research sites. Upon completion of the trial, the sponsor must adequately handle and store the data according to applicable ICH/GCP guidelines, trial SOP and regulations.

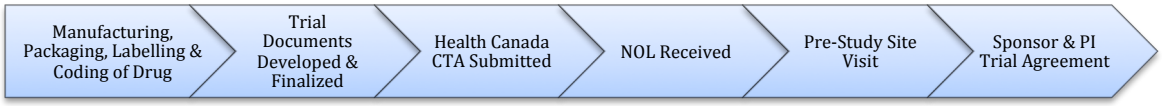

Figure 3 This timeline outlines the sponsor's responsibilities to set up a clinical trial prior to research participant enrollment.

9.2 Role of the Principal Investigator

Each research site has a PI, who is the physician responsible for trial conduct in order to protect the integrity, health and welfare of the subjects enrolled. The PI role and responsibilities in a clinical trial are outlined in Section 4.0 of the ICH/GCP guidelines. The PI must have education, training and experience in the area of medicine studied in the clinical trial (144). The PI's most recent CV must be available at the trial site to

support the educational and knowledge-based requirements. The PI must also be familiar the ICH/GCP guidelines, other applicable regulations and the investigational product. The PI should maintain records of the clinical trial agreement reached with the sponsor. Once the clinical trial agreement is in place, the PI will apply for ethics approval to the trial site's governing REB. Prior to an ethics submission the sponsor's consent form may require amendments to fulfill the needs of the trial site and target the patient population. Amendments must be communicated to the sponsor. Following ethics approval, the PI is responsible for all communications between the REB, the site and the sponsor.

Throughout the trial, the PI is responsible for the consent process, study drug management and assurance that the CRF are complete and available for monitoring and audits. The PI, or a sub-investigator, may manage trial-related medical care of a research participant if co-illnesses arise during enrollment. The PI must identify, define, manage and report adverse drug events to the sponsor, REB and regulatory authorities specified in the clinical trial agreement. Protocol deviations must be recorded and reported by the PI to the sponsor and REB. Overall, the PI is responsible for all site activities related to the clinical trial. Often, PI are conducting research in addition to their clinical practice, therefore it is unrealistic to conduct and manage all trial activities. A log should be maintained listing appropriately qualified persons whom the PI has delegated trial-related duties. The PI most often delegates responsibilities and tasks to the study site clinical coordinator.

9.3 Role of the Clinical Coordinator

The clinical coordinator is at the center of a research enterprise executing many trial duties and communications (145). The responsibilities of the clinical coordinator

have been critically examined due to the growth of clinical trials and demand for the position. Currently, the role of a coordinator is inconsistent among clinical sites and lacks clear job description (146). The ambiguity may be attributed to the fact that in recent years the position has evolved from a research assistant performing small delegated tasks into that of a true research coordinator, often a healthcare professional, who may function as a trial manager among other roles (147). The ICH/GCP guidelines do not reference or mention the clinical coordinator position at the study site failing to address the coordinator's role and responsibilities. Regulatory bodies, REB and sponsors often overlook the coordinator despite their centralized position (148). The coordinator is frequently delegated many of the PI responsibilities. These responsibilities include communicating with and preparing documents for the regulatory authority, REB and sponsor, as well executing trial formalities and direct interactions with study participants and the investigational product. Despite many responsibilities, research ethics boards and regulatory authorities do not require the identity or qualifications of the clinical coordinator. Disconnect between guidelines, regulatory expectations and actual trial conduct provides a clearly apparent need to formalize and clearly define the role and scope of a clinical coordinator.

The clinical coordinator's scope expands as registered professionals fulfill the role. Registered Nurses (RN) are the largest professional body occupying clinical coordinator positions, followed by Pharmacists (147). The increasing need for educated and qualified coordinators reflects the increasing number of clinical trials and the continually rising regulatory expectations (149). A coordinator must be factually detail-oriented with good problem solving and managerial skills. The experience and attributes

of an RN complement the requirements of a competent clinical coordinator. Registered Nurses are educated to think critically, prioritize needs and mobilize resources offering a unique contribution and holistic perspective to the role (150, 151). Registered Nurses also possess public trust, which may positively influence patient recruitment and retention.

Clinical coordinators have formal and informal education, knowledge and experience in study methodologies, ethical and practical issues, study management and data handling (152). Clinical coordinators may contribute to study design, protocol development, and interpretation of results as a part of the clinical trial team (150). The coordinator works in a centralized position between the PI, the sponsor, REB, regulatory and as an advocate for the research participant (145). The informed consent process is often delegated to the nurse coordinator due to his/her clinical ability and background (153). Strong interpersonal skills are essential for recruitment and retention of the research participants (148). The coordinator becomes the point of contact for the study participant and therefore often takes on the role of educator, mentor and advocate (154). A strong and well-qualified clinical coordinator contributes to the quality of data (155). Nurse coordinators are capable of monitoring research subjects for adverse events, dispensing medication per protocol, phlebotomy, and managing routine care issues. Providing holistic care to a research subject helps to build rapport, which may increase the likelihood of study adherence and retention.

Nurses are educated and experienced in physician-RN communication by discussing patient needs, addressing ethical or medical issues and independently carrying out orders and procedures. A clinical coordinator must develop an interdependent

working relationship with a study's PI to conduct a safe and efficient trial (149). Nurses value the social relations, technical/clinical skills and knowledge, work autonomy and control that clinical coordinating provides. Although the PI is ultimately responsible for the trial conduct, the coordinator is often managing the PI time and trial-related duties. A qualified nurse coordinator instills confidence in the PI and the sponsor while executing an organized and efficient trial.

A nurse coordinator may also be valuable with other personnel outside the research team. Studies may involve hospital staff such as nurses, physicians, phlebotomists and diagnostic technicians that view research and research related duties as a nuisance task to add to an existing heavy clinical workload (156). Nurse clinical coordinators can help change attitudes, educate on the importance of the trial and create a valued research environment. The coordinator may also be the hospital staff's point of contact for questions or trial-related issues that may arise. If the nurse coordinator fosters a positive relationship, the hospital staff may be more inclined to report pertinent information such as lab results and patient discharge times.

Proper training for PI and coordinators increases the trial's quality as well as the professional integrity of clinical research (157). Trial duties performed require the nurse coordinator to adhere to numerous research regulations and guidelines in addition to their own professional regulations which further emphasizes the importance of formal training and education (158). However many nurses working in clinical coordinator positions report learning the role "on the job" with little training (147, 159). Research sites are responsible for providing the clinical coordinator with formal research training and orientation to site-specific policies and procedures. It is also the responsibility of the

sponsor to ensure research sites are appropriately educating and orientating clinical coordinators due to their immense impact on the organization and progress of a trial. Nurses report being more satisfied with their job when they receive proper training and a clear description of their role (153). Nurses should seek clinical research associations for formal education, certification, resources and job support.

9.4 Clinical Research Associations

The Society of Clinical Research Associates (SOCRA) is a non-profit, charitable and educational membership organization committed to providing education, certification, and networking opportunities to all persons involved in clinical research activities (160). SOCRA workshops and conferences educates members in clinical coordinating, monitoring, SOP writing, investigator training, trial budgets, clinical research ethics and regulatory compliance in United States and Canada. Members can obtain the Certified Clinical Research Professional (CCRP) designation with a minimum two years full-time experience in any area of clinical research and upon passing the CCRP examination. The designation aims to promote recognition and continued excellence in the ethical conduct of clinical trials.

Although clinical research professionals come from a variety of backgrounds (clinical, business, statistics) and work in different research areas, they are governed by a common framework of guidelines and regulations. Important clinical trial and regulatory topics are included in the SOCRA CCRP examination. The exam is changed annually to ensure it is up-to-date with common practices and regulations. Similar to other professional designations, CCRP are required to complete education credits to maintain their designation and membership. The SOCRA source is a quarterly journal providing

recent issues, information and publications distributed to SOCRA members. A CCRP designation provides a clinical coordinator with the knowledge, competence and clear job requirements to set up, conduct and close a clinical trial.

The International Association of Clinical Research Nurses (IACRN) aims to enhance clinical research quality and safety through specialized nursing practice (161). The association provides support and education for RNs who directly or indirectly impact the care of research participants by advancing and advocating for clinical research nurses as a specialty practice. The IACRN has developed a scope and standards of practice to support and guide a nurse to work in the many facets of clinical research (162). The RN code of ethics and professional standards of practice combined with a clear research scope provides direction and support for a research nurse. A Registered Nurse with a CCRP designation, professional standards and experience can bridge clinical and research skill and knowledge to perform in different areas of clinical research and become a valued asset to any research team. The RN CCRP with specialized education in clinical trial conduct can function within an expanded role of a clinical coordinator, assuming more responsibilities and working on behalf of the PI. The expanded role of the clinical coordinator will be specifically valuable in investigator-initiated clinical trials, where the clinical research enterprise is smaller than the traditional large industry-driven trials. Within this expanded role, the clinical coordinator helps to manage the PI's time and responsibilities, which may also help the PI manage research and clinic time. A competent and high-functioning clinical coordinator instills confidence in the PI and positively affects trial conduct.

CHAPTER TEN

CONCLUSION

Clinical trials develop treatments to improve standards of care, enhance patient outcomes and increase quality of life. Evidence-based practice is the paradigm that emphasizes the explicit and judicious use of best research evidence currently available for medical decision-making (163). Evidence-based practice evolves as clinical research develops new pharmaceuticals, devices and biologics. Treatments must be extensively tested in lab preparations, non-clinical animal studies and clinical studies involving healthy volunteers (Phase I trials) prior to gathering efficacy data in target patient populations (164). In Canada, Health Canada's regulatory authority TPD and the governing REB critically examine each element of the study design and research protocol prior to granting approval. To protect the rights and well being of human subjects the study must adhere to ICH/GCP guidelines, Canada's Food and Drug Act and the TCPS. To ensure adherence to guidelines and regulations the sponsor provides quality assurance and control by monitoring trial site activities and promptly addressing issues. Health Canada audits confirms high caliber research conduct and regulatory compliance prior to subsequent stages of research and/or market authorization.

Clinical trials are responsible for the evolution of medicine and the possibility of new treatments and cures for illness and disease. Developing new treatments can be a long, tedious process delaying market authorization and ultimately patient outcomes because clinical research is a difficult, expensive and competitive business. In recent years, publication bias, selective reporting of findings, distorted interpretation of results and acts of bribery have cast a negative light on clinical trials and especially those

sponsored by large pharmaceutical companies (157). Conducting a clinical trial requires researchers to comply with stringent regulatory expectations. Regulatory authorities often request further information, research and background rationale to support the clinical study. Regulatory compliance is time-consuming and therefore, expensive. In addition to regulatory compliance, patent expiries set a strict time limit for pharmaceutical companies to conduct trials, obtain market authorization and gain a financial return on pharmaceutical sales before other companies market the generic drug. Professional integrity, valid and valuable study design, and study conduct excellence is essential to the success of a clinical trial, despite time and budget concerns. Sacrificing the quality of a clinical trial to manage and conserve time and money is detrimental to study outcomes and overall legitimacy of the trial.

Experiential learning was the basis of my graduate studies as I worked my way through the development and set up of a clinical trial. A small amount of didactic course work and workshops provided me some theoretical foundation and background to coordinate a clinical trial. However, there was no course work, workshop or readings that could prepare or guide me through protocol development, application processes, clinical trial setup and troubleshooting any obstacles along the way. Over the past four years I have learned how to start from a clinical trial idea, develop a protocol and other required documents, apply for and obtain required approvals and set up a clinical trial ready for participant enrollment, gaining all of the knowledge by doing. The learning and expertise that I have gained from interactions with the professionals inside and outside of my research team is beyond valuable. I have had the opportunity to work with personnel within different areas of the clinical trial industry such as the sponsor, manufacturer,

Health Canada, REB, contract research organizations and physicians and residents, each time taking away a new perspective or understanding that surrounds clinical research. I had the opportunity of travelling to Ukraine and working with a Ukrainian contract research organization. While I was in Ukraine I also had the opportunity to interact with physicians and other healthcare workers. This experience has also given me perspective on the similarities and differences of healthcare and clinical trial research in Canada and Ukraine. Over the course of my graduate studies I have obtained valuable experiential knowledge that will allow me to be a stronger and more effective clinical trial coordinator, RN and educator.

Educated, experienced and motivated research professionals are essential to fulfilling clinical trial expectations. Creating professional research environments and building sound research capacity will help to further advance medicine and evidence-based patient care. The RN CCRP brings professionalism, knowledge, skill and a holistic perspective to the ever-changing and competitive world of clinical research. However, regulatory expectations, ICH steering committee, REB, Sponsors and other stakeholders need to include the role of the clinical coordinator in guidelines and regulation to address the disconnect that exists between guidelines and regulations and actual trial conduct. Improving the existing guidelines and regulatory expectations to reflect realistic clinical trial site conduct and include enhancing the role of the clinical coordinator with additional education in the design, preparatory stages and execution of investigator initiated clinical trial will undoubtedly alleviate some of the PI's most demanding responsibilities, which we expect will result in more investigator-initiated research.

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Clinical Trial Protocol

A Proof of Concept Studyof L-Alanyl-L-Glutamine for the Reduction of Peritoneal Adhesions in Adult Females Undergoing Myomectomy

Protocol Number: Ade002-2013

Drug Name: L-Alanyl-L-Glutamine

Funder: AdeTherapeutics

Principal Investigator: Prof. A. Velygodskiy

Draft or Version Number: 1

Date of (Current) Protocol: August 19, 2013

CONFIDENTIAL

SIGNATURE PAGE

Protocol Number: **ADE**002-2013

Title of Protocol: A Proof of Concept Study of L-Alanyl-L-Glutamine for the Reduction of Peritoneal Adhesions in Adult Females Undergoing Myomectomy

Sponsor:

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(Name)	Date

Dr. Nikolai Nikitin, Director, RUSSLAN Clinical Research

(Name)	Date

PROTOCOL SUMMARY

Study Number and Title:	Ade002-2013: A Proof of Concept Study of L-Alanyl-L-Glutamine for the Reduction of Peritoneal Adhesions in Adult Females Undergoing Myomectomy
Clinical Phase:	Phase I
Study Objectives:	To test the null hypothesis that there is no significant difference in the extent and severity of adhesions following myomectomy in patients treated with L-Alanyl-L-Glutamine or placebo administered into the peritoneal cavity. To establish preliminary safety and tolerability of a formulation of L-Alanyl-L-Glutamine in Water for Injection, pH = 6, or placebo administered into the peritoneal cavity in humans at a dose of 1g/kg of body weight.
Primary Endpoint:	**The primary endpoint will be statistically significant reduction in adhesions observed in the L-Alanyl-L-Glutamine treated group compared to placebo at 6-8 weeks post-myomectomy. Based on the analysis approach described in 11. STUDY VARIABLES AND STATISTICAL ANALYSIS, the primary endpoint will be met if the Treatment group has a statistically significant fewer patients in the "Adhesions" category (and therefore, 30% more in the "Non-**

	Adhesions" category) compared to the Placebo group.
Study Design:	Subjects will have a diagnosis of uterine fibroids (myoma). Eligibility will be determined and informed consent obtained. 38 subjects will undergo a laparoscopic myomectomy and 10 subjects will undergo a myomectomy by laparotomy. The myomas will be diagnosed using ultrasound. The method of surgery will be determined by the surgeons' clinical judgment and may be based on the subject's medical and /or surgical needs and concerns. Reasons for opting for a laparoscopic or laparotomy approach may depend upon numerous factors such as, the medical suitability for laparoscopic surgery, the size of the myomas within the uterus and the location of myomas within the pelvis and abdominal cavity. The subjects will be randomly assigned to treatment (L-Alanyl-L-Glutamine) or placebo within each surgical method group. At the time of surgery, treatment (L-Alanyl-L-Glutamine) or the placebo will be delivered into the peritoneal cavity. The surgery is followed by standard hospital post-operation care. A follow-up laparoscopic evaluation will be done 6-8 weeks post-operation to determine the efficacy of the treatment (L-Alanyl-L-Glutamine). The study duration will be approximately twelve (12) months from first patient, first visit to last patient, last visit.
Study Population:	The sample size for this study is n = 48 ;24 subjects receiving the treatment (L-Alanyl-L-Glutamine) ;24 subjects receiving the placebo;10 subjects undergo a myomectomy by laparotomy. **Main inclusion criteria are:** - Subjects are female - Subjects are 18 years of age or older at the time of consent - Subjects have a BMI between 17-40 - Subjects must have signed informed consent form - Subjects have a preoperative diagnosis of uterine fibroids and plan to have a myomectomy completed surgically as part of their standard care - Subjects must have a physical examination and compliance assessment **Main exclusion criteria are:** - Subjects whose BMI is outside the range of 17-40 - Subjects participating in another clinical trial with a drug or device

	- Subjects who have participated in a clinical trial with a drug or device within 30 days prior to this study - Subjects with suspected or diagnosed pregnancy - Subjects with undiagnosed vaginal bleeding - Subjects with suspected intraabdominal infection - Subjects who are immunocompromised - Subjects diagnosed with cancer - Subjects treated with hemostatic agents (e.g. fibrin sealant, collagen, oxidized cellulose) - Subjects treated with adhesion prevention agents other than the Anti-Adhesion product (APP) (e.g. Intergrel® Adhesion Prevention Solution, Seprafilm® - Membrane) - Subjects taking anti-epileptic medications - Subjects who have been treated with Methotrexate or other chemotherapeutics agents - Subjects with an American Fertility Society score of Stage D at the time of myomectomy as determined by the surgeon
Study Treatment:	**Activity:** The active substance is L-Alanyl-L-Glutamine. It enhances wound healing and plays a role in stress response through muscle repair, maintenance of digestive health, and in the modulation and function of neutrophils, macrophages and lymphocytes. **Dosing:**1g/Kg body weight of L-Alanyl-L-Glutmine, applied to the peritoneum at a concentration of 400mg/mL in water for injection(WFI), pH=6, 20mL in a 20mL vial. **Safety:**Based on rat studies, in which the product L-Alanyl-L-Glutamine, formulated as described above and dosed in the range of 0.3g/kg of body weight to 1.5g/kg of body, no toxicities or adverse effects at any of the doses tested were observed. In humans, L-Alanyl-L-Glutamine is a well-characterized nutritional supplement. It has been used widely in Total Parenteral Nutrition and has been dosed parenterally and enterally in a hospital setting in critically ill patients with no adverse effects noted. **Efficacy:** The ability of the product L-Alanyl-L-Glutamine to reduce post surgical adhesions as proposed above will be determined during the 8-week post-operation follow up laparoscopic examination. Both the incidence and the severity of adhesions will be assessed. The incidence of adhesions will be determined visually. Digital recording of all surgeries and sites where the uterine surface was opened/incised/cauterized/sutured will be compared between first and second surgeries. Severity of the adhesions will be assessed using the AFS (American Fertility Society) scoring system, which evaluates the extent and aspect of adhesions at four anatomical sites, right ovary, right tube, left ovary, left tube. All findings will be recorded in the subject's case report form (CRF).

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ABBREVIATIONS AND DEFINITIONS

AE(s)	Adverse event(s)
AG	L-Alanyl-L-Glutamine
ANC	Absolute Neutrophil Count
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CR	Complete Response
CRF(s)	Case Report Form(s)
CXR	Chest X-Ray
EC	Ethics Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous

kg	Kilogram
L	Litre
m^2	metre squared
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mg	milligrams
min	minutes
mL	milliliter
NSAID	Non-Steroid Anti-Inflammatory Drugs
PI	Principal Investigator
PK	Pharmacokinetics
RBC	Red blood cells
SAE(s)	Serious adverse events
TPN	Total Parental Nutrition
WBC	White blood cells
WFI	Water for injection

1. INTRODUCTION AND BACKGROUND

1.1 Adhesion Formation

Adhesions are abnormal deposits of fibrous tissue that form within the peritoneal cavity. The peritoneal cavity, intra-abdominal and pelvic organs are encased by an epithelial membrane called peritoneum. Blood, lymph, vessels and organ tissue lie beneath peritoneal surfaces (Tortora, 1984).

Adhesions form as a result of fibrous repair of peritoneal injury mostly after surgery or infectious processes (Menzies, 1992, Bridges, Johnson &Whitting, 1965). Adhesion formation begins with injury inflicted on the peritoneum by an injurious stimulus. These stimuli can include bacterial infection, inflammation, chemical toxicity, ischemia, and mechanical injury or simply drying from exposure to air (Drollette&Badawy, 1992, Dijkstra et al., 2000). The injury leads to an inflammatory response, which progresses to fibrin deposition and subsequent fibrinous adhesion.

Adhesion formation may occur after any surgical procedure, following infection and inflammatory conditions; however, it is extremely common after abdominal and pelvic surgical operations and remains a source of considerable morbidity. The incidence ranges from approximately 67%-93% after general surgical abdominal operations and up to 97% after open gynecologic pelvic procedures (Menzies& Ellis, 1990, Parker et al., 2001). In clinical and autopsy studies of patients who had prior laparotomy, the incidence of intra-abdominal adhesions was about 70-90% (Ellis, 1982).

Adhesion formation is common following myomectomies or surgeries that damage the surface of the uterus (Pal, 2011). Despite existing adhesion treatments and barriers, adhesion formation remains a challenge following uterine surgeries (Tinelli et

al., 2011). Due to the adhesions that form following myomectomies (regardless of the modality for completing the surgery), a second laparoscopic surgery is often completed to remove scar tissue that may interfere with fertility.

While it is believed that laparoscopic surgeries reduce the formation of de novo adhesions (DeWilde&Trew, 2007), a meta-analysis revealed comparable results for laparotomy vs. laparoscopic surgery for both formations of de novo adhesions and reformation following adhesiolysis (Wiseman, Trout & Diamond, 1998). When comparing laparotomy and laparoscopic gynecological procedures, the risks of adhesion-related complications are similar (Lower et al., 2004). Abdominal adhesions that form within the peritoneal cavity are a common cause of small bowel obstruction and female infertility (Thompson &Whawell, 1995, Thompson, 1995, J SurgSuppl, 1997).

1.2 Background of Treatment Options

Various methods of adhesion prevention have been employed, including prevention of fibrin deposition in the peritoneal exudate, reduction of local tissue inflammation, and removal of fibrin deposits (Vipond et al., 1990). Most of the existing methods inhibit only one of these mechanisms and have had limited success. Physical barriers aimed at preventing the formation of adhesions have included implants in the form of resorbable fabrics or membranes have been considered as macrophage barriers. Gels formed of biocompatible materials have also been employed to reduce formation of adhesions. Examples of these barrier methods are the products sold under the trademarks INTERCEED® and SEPRAFILM®. Surgical mechanisms include atraumatic tissue handling, infusion of large quantities of fluids, such as saline. Alternatively hyperosmotic fluids have been explored as a means to increase intracavitary fluid collection. Each method for adhesion prevention has had limited success.

1.3 Summary of Nonclinical and Clinical Data

1.3.1 AdeTherapeutics Trials

a.) Studies in Humans

AdeTherapeutics obtained approval on 24/11/2011 by Health Canada Therapeutic Products Directorate to conduct a similar study in humans entitled "A Randomized, Double-Blind, Placebo Controlled Phase I Study of L-Alanyl-L-Glutamine For the Reduction of Peritoneal Adhesions in Adult Females Undergoing a Laparoscopic Salpingostomy for the Removal of an Ectopic Pregnancy"under contol#149291, Protocol # Ade001-2011. The trial in Canada will evaluate preliminary safety and efficacy in humans of the same novel formulation and atypical route of administration of L-Alanyl-L-Glutamine proposed in the present protocol for the prevention of post surgical adhesions.

b.) Studies in Animals

AdeTherapeutics acquired the rights to non-GLP proof of concept studies conducted by Dr. Adebola Obayan, M.D., Ph.D., under Animal Research Ethics approval at the University of Saskatchewan. Dr. Obayan later became CSO of AdeTherapeutics. In these studies, L-Alanyl-L-Glutamine was administered intraabdominally to rats for reduction of adhesions following abdominal surgery. The results indicate that L-Alanyl-L-Glutamine reduces the incidence and severity of adhesions in animals treated with the drug at the time of surgery, as compared to animals treated with saline only or animals that did not receive either treatment or vehicle. In one definitive study, male Wistar rats (n=70) were divided into five groups corresponding to three Treatment and two Control groups. The Treatment groups underwent open surgery that involved a midline sub-umbilical incision and a modified cecal puncture with purse string repair. L-Alanyl-L-Glutamine (0.3g/kg-1.5g/kg); saline (5ml); or L-glutamine (1.5g/kg) was instilled into the abdominal cavity from a syringe just prior to closure of the abdominal incision. Control Group 1 was comprised of animals on whom no surgery was done (virgin abdomen). Control Group 2 was comprised of animals that received surgery but did not receive drug or placebo at the time of closure.

Ninety days following surgery, a repeat laparotomy incision was completed. The animals in all five groups were reopened by midline sub-umbilical incision. The abdominal cavity was inspected visually for incidence and severity of adhesions. A Zuhlke score (Zuhlke et al., 1990) was applied to estimate severity of the adhesion (Grade 0 – no adhesion, Grade 1 – flimsy adhesion, Grade 2 – mild adhesion, Grade 3 – moderate adhesion, Grade 4 – severe adhesion). Animals were sacrificed to evaluate the abdominal organs for histopath evidence consistent with inflammation and adhesions. The process of acute inflammation was assessed based on the immunohistochemical detection of MCP1 (macrophage chemotactic protein) and the number of macrophages. The average number of milky spots per high-powered field was determined as well. Milky spots (composed of macrophages, B-lymphocytes and leucocytes) are indicative of adhesion formation. Fibrosis and collagen formation were also assessed.

The results of the visual scoring indicated that adhesions in L-Alanyl-L-Glutamine treated rats were absent or reduced by about 80% ($p \leq 0.05$) following abdominal surgery compared to saline or untreated controls. Histological examination revealed that fibrosis and collagen formation assessed ten days after surgery were significantly reduced in animals treated with L-Alanyl-L-Glutamine or L-Glutamine. The level of MPC1 expression and macrophage number tended to be reduced in rats treated with A-G or L-Glutamine compare to untreated animals or rats treated with the saline solution, although this was not a statistically significant observation. No complications, including deaths, were observed in the group of rats treated with L-Alanyl-L-Glutamine compared to the surgical control groups (i.e., no treatment, saline

only treatment). Animals were evaluated for adverse effects as per standard, well defined metrics for signs of distress or discomfort established specifically for rats.

The results of this non- GLP animal study support the hypothesis that L-Alanyl-L-Glutamine, administered intra-abdominally, just prior to closure of the surgical wound, is effective at reducing or preventing abdominal adhesions that typically arise following surgery. These results also indicate that a formulation of L-Alanyl-L-Glutamine in Water for Injection, not buffered to physiological pH and not isosmotic, is well tolerated in the rat.

1.3.2 Scientific Literature

a) Safety Studies in Animals

Oda et al (2008) studied the acute and subchronic toxicity of L-alanyl-L-glutamine in Sprague- Dawley rats. Three treatment groups received L-alanyl-L-glutamine as 1%, 2% and 5% of their diet. After 14 days there was no toxicological effects observed. After 13 weeks there was no difference in the toxicological effects between the treatment group and the control group with respects to body weight gain, feed consumption and efficiency, ophthalmological, hematological, clinical chemistry and urinalysis. Tsubuku et al. (2004) conducted a safety study on 75 Sprague-Dawley rats. Glutamine, as dietary supplement, was administered over a period of 13 days. Glutamine was supplemented at 1.25%, 2.5% and 5% of the standard diet. The control group received the standard diet only. The rats studied displayed no changes in diet consumption, ophthalmologic findings, gross pathology and histopathology. During measurements of urine parameters, alteration of total protein and urine pH, ketone bodies

were detected in the groups receiving 2.5% and 5% of glutamine. Several haematology parameters such as platelet count, hemoglobin, and lactate dehydrogenase increased in the group of rats receiving 5% of glutamine. However, these changes remained in the physiological range. Olney et al (1971) investigated cytotoxic effects of different amino acids on the brain and retina of infant mice. Ten-day-old Webster Swiss albino mice were given 24 different compounds in the form of a single subcutaneous dose. Integrity of cellular structures of the brain and retina were sassed by light and electron microscopy. L-glutamine was shown to have no cytopathic effect at the dose of 12 mmol/kg (1.75 g/kg) and weakly toxic at the dose of 24 mmol/kg (3.5 g/kg) that resulted in the necrosis of a small number of neurons. This group of rats also showed no cytotoxicity in the explants of the peritoneum.

b) Pharmacokinetic Studies in Animals

Adibi et al (1989) conducted a study to test the safety of alanyl-glutamine in rats. A dose of 0.5umol/g was given through IV injection into a taill vein. The rats were monitored over 15 minutes post injection and blood samples were taken at 0, 2, 4, 6 and 10 min post injection. Blood samples suggested a half-life of 0.7 min +/- 0.1 min and a renal route of excretion. Abumrad et al (1989) investigated the clearance of glycyl-glutamine and alanyl-glutamine by liver, kidney, gut and muscle tissue in 18 hour fasted dogs. Dipeptides were injected at the rate 12 micro-mol/min/kg. Plasma concentration was higher for glycyl-glutamine 1,113 ± 57 micro-mol vs. 308 ± 17 micro-mol for alanyl-glutamine. Metabolic clearance excretion rate was higher for alanyl-glutamine comprising 40.2 ± 2.6 ml/min/kg vs. 11.0 ± 0.5 ml/min/kg for glycyl-glutamine. The

liver and kidney were involved in the metabolic clearance of alanyl-glutamine at similar rates, which were approximately two times higher then those for gut and muscle. In another study, metabolism of the highly soluble solution of radioactively labeled alanyl-glutamine was administered by intravenous to rats (Stehle, 1989). Three hours after bolus administration the amount of recovered alanyl-glutamine was 56% in CO2, 13% in muscle, 3.1% in liver, 1.9% in plasma and 0.6% in kidney of the injected dose. Stehle found that alanyl-glutamine was hydrolyzed immediately and is, therefore, a suitable source of glutamine.

c) Safety Studies in Humans

Numerous studies are available in the literature describing L-Alanyl-L-Glutamine treatment of critically ill patients. Jiang et al. compared parenteral alanyl-glutamine (treatment group) and normal TPN (control group) in a double blind study of 120 post-operative patients (Jiang, 1999). The treatment group received 0.5g/kg of alanyl-glutamine per day. No significant differences were found between the two group's blood panels. Morlion et al., (1998) looked at the safety of alanyl-glutamine as part of a TPN infusion. Twenty-eight subjects received 0.3g/kg of alanyl-glutamine over 5 days post-operatively after abdominal surgery. No side effects or patient complaints were reported. Patients who received the alanyl-glutamine TPN infusion had improved nitrogen balance, improved lymphocyte recovery on day 6 and improved generation of cysteinyl-leukotrienes from polymorphonuclear granulocytes. Roth (2008) evaluated a dose of 30-40g/70Kg of body weight delivered through parental and enteral routes to prevent glutamine deficiency in critically ill patients. There were no observed toxicities

in this study. A phase I pharmacokinetic study used doses up to 0.65g/Kg orally in pediatric oncology patients (Ward, 2003). This treatment was well tolerated with no untoward plasma glutamine or ammonia levels. Exner (2003) used L-Alanyl-L-Glutamine in an intravenous infusion preoperatively to reduce the patient's susceptibility to infection and sepsis. A dose of .5/Kg/24 hours over a 72 hour infusion was studied and was well tolerated.

Lowe et al (1999) studied the effects of a glutamine supplemented TPN infusions in 7 healthy volunteers. The study was conducted over three 5-day periods with increasing glutamine doses (0, 0.285 and 0.570 g/kg). All diets were well tolerated with no adverse effects. Plasma glutamine concentrations increased significantly but plateaued at concentrations approximately 25% above control values. Ammonia and glutamate, potentially toxic metabolites of glutamine, had no significant changes following glutamine enrichment. This study demonstrated that glutamine-enriched TPN was well tolerated with no associated signs of toxicity when given parenterally to healthy volunteers.

Reports of adverse effects associated with glutamine treatment in humans have been rare. Hornsby Lewis, et al, 1994 did observe that glutamine in TPN infusions may cause hepatic toxicity. However this effect was reversible upon termination glutamine treatment. The study involves 7 stable patients who received daily home TPN solutions supplemented with 0.285 g/kg of glutamine for four weeks. Five patients received the full 4 weeks of glutamine-TPN. In two patients, TPN infusions were stopped at the end

of week 2 and 3 due to elevations in liver enzymes. Liver enzymes returned to normal range with the discontinuation of the glutamine supplementation. While the investigators cautioned against the use of glutamine on home TPN treatment, further evaluation is needed.

d) Pharmacokinetic Studies in Humans

Albers et al (1998) assessed the pharmacokinetic effects of alanyl-glutamine in 10 healthy individuals. A bolus intravenous infusion was given over 30 minutes at a dosage of 30mg/kg bodyweight. The elimination half-life was 3.8 minutes and the volume of distribution was 10.52 L. In another study, Ziegler (1990) compared two doses of alanyl-glutamine, 0.3 mg/kg body weight and 0.1mg/kg body weight, administered by bolus intravenous infusion to four healthyindividuals. The elimination half-life of alanyl-glutamine for this study was reported as 12 ± 2 minutes for the initial phase and 67 ± 11 minutes for the terminal phase, a volume of distribution of 14.7 ± 2.1 L and clearance rate of 2.3 ± 0.5 mg/kg/min.

e) Combined Safety and Efficacy Studies of Intraperitoneal L-Alanyl-L-Glutamine

A Phase II study to evaluate the feasibility and safety of theaddition of alanyl-glutamine-dipeptide todialysis solutions in Peritoneal Dialysis (PD) patients is currently in progress at the Medical University, Vienna, Austria. The study, which was authorized on January 14, 2013 and is registered on *ClinicalTrials.gov* is proceeding under EudraCT Number 2012-004004-36. In this trial, L-Alanyl-L-Glutamine is being administered to

human dialysis patients at two different concentrations, 8 millimolar and 16 millimolar in peritoneal dialysis solution. No results for this study have been reported as yet.

1.4 Risks and Benefits to Human Patients

Please refer to the Investigator's Brochure.

2. RATIONALE

2.1 Rationale for the Study

Glutamine is a conditional essential amino acid that the body is unable to synthesize in sufficient quantity under certain physiologic circumstances (Smith, 1990, Lacey & Wilmore, 1990). These circumstances include major surgery, shock, traumatic injury and severe sepsis. A decrease in extracellular glutamine impairs the function of macrophages and other immune cells, resulting in increased protein degradation from skeletal muscle (Vinnars, Bergstom&Furst, 1975). Although glutamine constitutes more than fifty percent of the unbound amino acid pool in human skeletal muscle, rapid reduction in blood and tissue glutamine has been noted following catabolic events such as major surgery (Askanazi et al., 1980), trauma (Roth, 1985), and sepsis (Roth et al., 1985). Glutamine is safe and well absorbed in the body.

Glutamine dipeptides have been used for parenteral and enteral supplementation components in critically ill patients. In a randomized prospective study, Morlion et al. (1998), using glutamine dipeptides in total parenteral nutrition (TPN), concluded that the supplement group had a shorter hospital stay, improved immune status and improved nitrogen balance after abdominal surgery (Morlion et al., 1998). Enteral supplementation with alanyl-glutamine, (but not glutamine + alanine mixture), promoted intestinal adaptation as evidenced by increased peptide transport after intestinal resection (Liakakos

et al., 2001). Alanyl-glutamine also prevents intestinal damage, as demonstrated by increased peptide transport absorption expression and an elevated plasma glutamine concentration after cyclophosphamide administration (Satoh et al., 2003). Alanyl-glutamine alone was recently used enterally in post-operative patients for the first time with reported success and safety (Satoh et al., 2003).

L-Alanyl-L-Glutamine in water for injection (WFI), applied directly to the peritoneum at the close of surgery, is a novel treatment for the prevention of post-operative adhesions. Pharmaceutical grade L-Alanyl-L-Glutamine is commercially available and is covered under a Drug Master File (DMF) (Letter of Authorization available). L-Alanyl-L-Glutamine is metabolized to L-Glutamine and L-Alanine following administration. The dipeptide has a higher solubility and chemical stability than either glutamine or alanine alone, making it a more stable source of glutamine. L-Alanyl-L-Glutamine is administered intra-abdominally prior to closure of the surgical wound. This treatment is expected to prevent or significantly reduce adhesion formation that can form as a result of abdominal or pelvic surgery.

2.2 Rationale for Drug Dose Selection

The Proof of Concept study proposed herein will be the first in man using L-Alanyl-L-Glutamine in Water for Injection, adjusted to pH=6, administered to the peritoneum at the close of abdominal surgery in humans. As noted in the foregoing, L-Alanyl-L-Glutamine itself is well tolerated at various doses in humans with no observed toxicities or adverse effects regardless of route of administration studied. While we acknowledge that phase I studies typically are conducted on healthy normal subjects, because the proposed study involves conducting pelvic surgery on the trial participants,

however, we cannot, for ethical reasons, conduct this type of study in healthy, normal subjects.

A wealth of data exists in the literature supporting the safety of L-Alanyl-L-Glutamine itself in humans in doses up to 1.5 g/Kg cumulative dose (Exner, 2003), preliminary dose finding or identification of a maximum tolerated dose of L-Alanyl-L-Glutamine in humans prior to conducting this Proof of Concept study, therefore, did not seem necessary. The proposed 1.0 g/Kg dose represents the midpoint of the range(0.3 – 1.5g/kg of body weight) used in the non-GLP proof of concept studies in rats. It is also well within the dose range reported in the literature. As such, it represents an acceptable balance of proving the concept versuspotential for tolerability issues with AdeTherapeutic's novel formulation and atypical route of administration.

While no safety signals from the active pharmaceutical ingredient itself, L-Alanyl-L-Glutamine are expected, nor would the treatment volume of approximately 10% of total peritoneal volume be expected to impact tolerability, the tolerability of the formulation as a whole combined with the atypical route of administration, needs to be established in humans. The AdeTherapeutics formulation is comprised of WFI adjusted to pH = 6. This composition would be substantially different from the reported isosmotic, pH neutral formulations used in humans to date. Although it has been established in a clinical setting that hyperosmotic dialysis solutions can be damaging to the peritoneal membrane (Kratochwill et al., 2012), there is no data regarding the inverse: the effect of hypo-osmotic and lower pH solutions, such as the AdeTherapeutics formulation, on the peritoneal membrane.

In summary, Ade Therapeutics proposes to conduct this first in man, Phase I study to establish preliminary efficacy and safety of the L-Alanyl-L-Glutamine formulation as a whole, administered via an atypical intraperitoneal route to human surgical patients. The single dose of 1 g/Kg body weight selected for this study represents the approximate mid point of the range of AdeTherapeutic's proof of concept studies in rodents and is well within the range of tolerated doses in humans as described in the literature. This first study in humans of the AdeTherapeutics formulation and atypical route of administration of L-Alanyl-L-Glutamine is designed to confirm the results obtained in the non-GLP rat studies previously conducted by Dr. Obayan as described earlier.

3. STUDY OBJECTIVES

3.1 Primary Objective

To test the null hypothesis that there is no significant difference in the extent and severity of adhesions 6~8 weeks following myomectomy in patients treated with intraperitoneal administration of L-Alanyl-L-Glutamine at a dose of 1g/Kg body

weight, versus placebo, placed immediately after myomectomy, just prior to closure of the surgical incision.

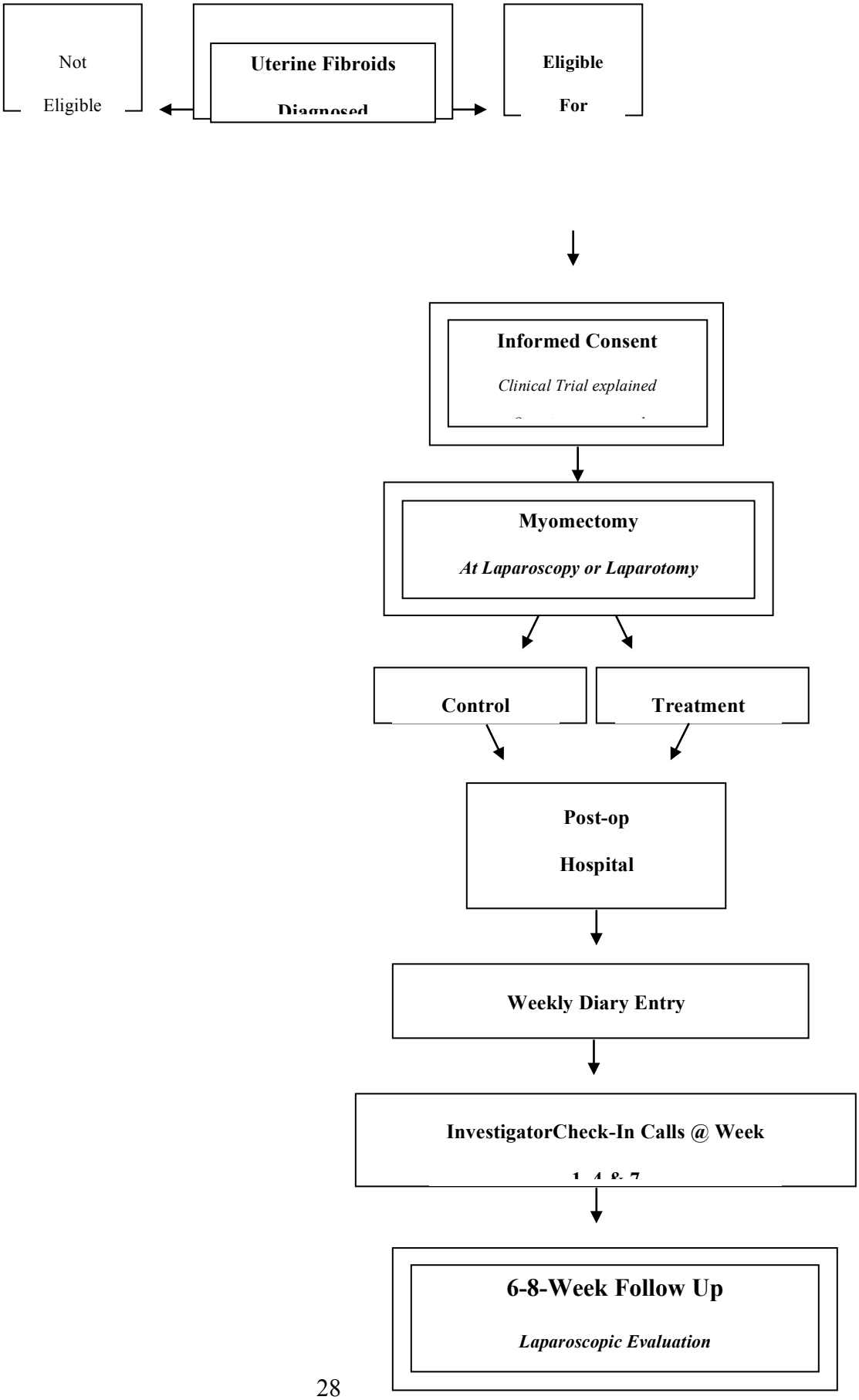
3.2 Secondary Objective(s)

To establish preliminary safety and tolerability in humans of a formulation of L-Alanyl-L-Glutamine in Water for Injection, pH = 6 , administered into the peritoneal cavityat a dose of 1g/kg of body weight.

4. INVESTIGATIONAL PLAN

4.1 Basic Design Characteristics

Study Design



4.2 Discussion of Study Design

This study will be a randomized and double-blinded, using placebo as comparator. Subjects will be adult females diagnosed with uterine fibroidswho are undergoing a myomectomy as part of standard care. Uterine fibroids are most commonly diagnosed by clinical examination with confirmation by transabdominal or transvaginalultrasound examination. Once uterine fibroids have been diagnosed and eligibility has been determined, the subjects will sign the informed consent form prior to admission into the trial. Forty-eight (48) eligible subjects will be enrolled in the dose treatment panel and randomly assigned (double-blind allocation) to receive L-Alanyl-L-Glutamine or placebo .Thirty-eight (38) subjects will undergo a laparoscopic myomectomy and 10 subjects will undergo a myomectomy by laparotomy. The method of surgery will be determined bythe surgeons' clinical judgment and may be based on the subject's medical and /or surgical needs and concerns. Reasons for opting for a laparoscopic or laparotomy approach may depend upon numerous factors, such as the medical suitability for laparoscopic surgery, the size of the myomas within the uterus and the location of myomas within the pelvis and abdominal cavity. The subjects will be randomly assigned to treatment or placebo within each surgical method, (laparoscopy or laparotomy).

Two different types are surgery (laparoscopic and laparotomy) will be evaluated in order to optimize the experimental methodology. Different surgical procedures may be better suited to the experimental approach for proving the concept proposed. While either surgical type will accomplish the myomectomy, they may not both elicit adhesions to the same extent. The results of the study could be skewed if the type of surgery employed does not elicit adhesions, which could result in a false lack of effect for L-Alanyl-L-Glutamine as compared to placebo treated patients. Therefore, this first phase I, proof of concept study involves both types of surgery to determine an appropriate surgical model to effectively test our novel therapeutic approach.

At the beginning of the surgical procedure, prior to myomectomy, pictures will be taken of the reproductive organs to enable an assessment of pre-existing scar tissue (adhesions). Any subjects who have an American Fertility Society score of Stage D, as determined by the surgeon, will be eliminated from the study.

After the surgery, each subject will be admitted into a surgical ward and monitored according to standard in-hospital post-operation care. Upon discharge, subjects will be given a diary card and required to make weekly entries by answering a number of questions. The Study Investigator will conduct check-in telephone calls to each subject 1, 4 and 7 weeks post-surgery.

At 6-8 weeks post-myomectomy surgery, the subject will report back to the hospital for a "second-look laparoscopic surgery". Pictures will be taken at surgery to assess and score the incidence and severity of adhesions. Adhesiolysis will be performed on any adhesions noted according to standard care and according to the surgeon's clinical judgment. Adhesiolysis is not part of the study protocol.

Each of the study treatments (study drug vs placebo) will be treated independently. The subject will be required to attend a standard post-operative follow-up appointment according to standard care.

The duration of the study will be approximately twelve months from first patient--first visit to last patient--last visit. The duration for each subject will be six to eight weeks, from time of the myomectomy to the second-look laparoscopic procedure.

4.3 Primary Endpoint

The primary endpoint will be statistically significant reduction in adhesions observed in the L-Alanyl-L-Glutamine treated group compared to placebo at 6-8 weeks post-myomectomy. Based on the analysis approach described in 11. STUDY VARIABLES AND STATISTICAL ANALYSIS, the primary endpoint will be met if the Treatment group has a statistically significant fewer patients in the "Adhesions" category (and therefore, 30% more in the "Non-Adhesions" category) compared to the Placebo group.

4.4 Rationale for Population Selection

Uterine fibroids are a common disorder in women during their reproductive years with an incidence between 20% and 50% (Dessolle et al., 2001). Uterine fibroids will increase the size of the uterus and may lead to menorrhagia, dyspareunia, urinary frequency and incontinence. Uterine fibroids have been associated with pelvic pain as the fibroids/uterus create pressure on adjacent pelvic and abdominal structures (Luciano, 2009). Uterine fibroids also have implications related to fertility. Typical therapy for uterine fibroid related complaints include hormonal therapies to regulate menstruation, gonadotropin releasing hormone agonist therapy to temporarily reduce the size and vascularity, myomectomy completed by laparoscopic or open laparotomy surgery, uterine artery embolization and hysterectomy. Myomectomy is preferred when there is a desire for preservation of fertility or as a personal choice to avoid hysterectomy and its potential complications (Takeuchi et al., 2008)(Horng et al., 2012). Uterine myomectomies performed laparoscopically or at laparotomy require that an incision is made through the

uterine serosa to expose the underlying fibroid for excision. Following the myomectomy, intramural suturing is typically needed to reapproximate the remaining uterine muscle. Suturing is typically completed to reapproximate the edges of the incised uterine serosa to decrease the formation of adhesions.Some investigators have used anti-adhesion barriers in an attempt to decrease the formation of adhesions (Ward &Panitch, 2011).Laparoscopic surgery is often scheduled to evaluate for and remove scar tissue especially when the initial indication for myomectomy surgery involves infertility or if pelvic pain occurs following myomectomy (Tulandi, Murray, &Guralnick, 1993)

4.5 Rationale for Second-Look Surgery

A second look laparoscopy is considered a component of standard patient care when the opportunity for the development of adhesions is high or when other pathological states warrant further surgical evaluation.

A second-look surgery is mandatory for this study and necessary to obtain efficacy data on the trial therapy. According to the Federal Drug Act (2002), second look surgeries are currently the primary modality for assessing adhesion formation/reduction in the abdomen or pelvis. Any adhesions present at the time of the second-look surgery will be photographed, assessed and scored prior to removal (adhesiolysis).

Adhesions affect up to 97% of gynecological pelvic procedures (Menzies& Ellis, 1990; Parker et al., 2001). Adhesions commonly cause bowel obstruction, pelvic pain and female infertility. Participants in this study who receive the active treatment could

potentially benefit by preventing the formation of adhesions; it is anticipated that the adhesion prevention therapy evaluated in this study will allow for the development of a superior method and become a standard of care for all patients undergoing gynecological surgery.

Adhesiolysis will be performed on any adhesions found during the second-look surgery, which would also be beneficial for any subjects participating in the trial.

5. SELECTION AND WITHDRAWAL OF Subjects

5.1 Number of Subjects

A total of 48 subjects will be enrolled in this study.

5.2 Inclusion Criteria

To be eligible for the study, subjects must fulfill all of the following criteria:

1. Subjects are female
2. Subjects are 18 years of age or older at the time of consent
3. Subjects have a BMI between 17 and 40
4. Subjects must have signed informed consent form
5. Subjects have a preoperative diagnosis of uterine fibroids diagnosed by ultrasound and plan to have a myomectomy as standard care. There are no restrictions on the number, size or location of fibroids. These characteristics may influence the surgeon's decision to perform the myomectomy at laparoscopic or laparotomy.
6. Subjects must have a physical examination and compliance assessment

5.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Subjects whose BMI is outside the range of 17 - 40
2. Subjects participating in another clinical trial with a drug or a device
3. Subjects who have participated in a clinical trial with a drug or device within 30 days prior to this study

4. Subjects with suspected or diagnosed pregnancy
5. Subjects with suspected intraabdominal infection
6. Subjects who are immunocompromised
7. Subjects diagnosed with cancer
8. Subjects treated with hemostatic agents (e.g. fibrin sealant, collagen, oxidized cellulose)
9. Subjects treated with any intraabdominal adhesion prevention agents including Anti-Adhesion Product (APP) (e.g. Intergel® Adhesion Prevention Solution, Seprafilm® Membrane)
10. Subjects taking anti-epileptic medications
11. Subjects who have been treated with Methotrexate or other chemotherapeutic agents
12. Subjects with an American Fertility Society score of Stage D at the time of myomectomy as determined by the surgeon

5.4 Withdrawal of Subjects

Subjects may voluntarily withdraw for any reason. Subjects may be withdrawn because of the appearance of a new health condition suspected to require medications prohibited by the protocol, unacceptable adverse events, refusal to continue treatment, or at the Investigator's discretion.

If a subject withdraws from the study at any time, the reason(s) for withdrawal must be recorded on the relevant page of the subject's Case Report Form (CRF); however the subject may withdraw from the study without providing a reason. Subjects discontinuing treatment will receive standard of care treatment from their primary physician, as necessary.

It is vital to obtain follow-up data on any subject withdrawn because of an adverse event. Every effort will be made to undertake protocol-specified safety follow-up procedures. If a subject discontinues participation due to an adverse event, the event will be followed until resolution or until the event becomes chronic. If a subject refuses to continue study procedures, the reason for refusal, if provided by the subject, will be fully documented in the subject's source document and recorded in the study specific CRF.

6. RANDOMIZATION AND BLINDING PROCEDURES

6.1 Randomization

Once subjects have been deemed eligible for the study and have consented to participate they will be assigned to either the treatment or placebo group. Randomization

of treatment assignment will increase the likelihood that any unrecognized differences between the two groups will be balanced. Randomization will be done with a permuted-block size of six to reduce likelihood of obtaining unbalanced study groups. Block randomization will be used to assure equal sample sizes to control for variation over time and to allow for truncated recruitment if necessary.

6.2 Blinding

The trial will be double blind and will remain blinded until the completion of the follow-up visit for the last subject and all data have been collected and analyzed. The investigators and subjects will remain blinded to the treatment allocation to which they are assigned, to reduce the chances of biased assessment of subjective outcomes. To preserve blinding of the treatments, the medication will be packaged off-site and delivered with appropriate labels to the study site. A clinician will use pre-packaged medication that will be labeled as Treatment A or Treatment B. Investigators and surgeons are blinded and therefore unaware of what A and B are. Each, (A and B,) have the potential of being either study drug (L-Alanyl-L-Glutamine) or placebo (saline). The study blinding procedures and subject randomization will be the responsibility of Dr. Hyun J. Lim from the Clinical Research Unit in the College of Medicine at the University of Saskatchewan. The list matching subject initials names to the unique identifying code will be sealed and stored in a locked cabinet in the AdeTherapeutics office and Dr. Lim's office. Dr. Lim is working as a consultant for AdeTherapeutics. The study manager will be un-blinded to facilitate shipment, storage and dispensing of investigational product. The study coordinator will also be responsible for preparing investigational product for use using the proper calculation based on the subject's body weight.

7. STUDY TREATMENTS

7.1 Supply, Packaging, Labeling and Storage

7.1.1 Drug/Placebo

Study drug/Placebo will be supplied in packages of 2 or 3 vials to permit accurate dosage of each patient as well as to prevent wastage of study supplies. The vial packs will be stored as per recommended label storage conditions at the site where surgery will take place and they will be labeled either "A" or "B". The placebo will be manufactured in Ukraine by YuriaPharm.

The study drug will be transported at the recommended storage temperature between 2 -8 degrees Celsius. Data loggers will be used for transport. The product will then be stored in a refrigerator set between 2 -8 degrees Celsius according to the product label recommended storage conditions. Labeling will be performed according to Ukrainian law. The placebo will be transported at the recommended storage temperature of room temperature. The placebo will be stored at room temperature according to the product label recommended storage condition. Labeling will be performed according to Ukrainian law.

7.1.2 Devices (surgical instruments)

All devices used are commercially available materials commonly found in hospitals and operating rooms.

a) A 14 FR x 16 inch catheter will be used as the drug delivery system. A luer lock adapter will be placed at the top of the catheter. This drug delivery system will be placed through the laparoscopic t instrument port. A laparoscopic grasper will be used to direct the drug delivery system

and ensure that the drug is evenly distributed to the surgical site where the uterine serosa has been incised.

b) A 14 FR blunt needle or intravenous plastic catheter attached to a syringe containing the study drug will be used as the drug delivery system when myomectomy is completed at laparotomy. The drug will be applied evenly to all surfaces where the uterine serosa has been incised.

c) Sterile syringes for administering the treatment through the port(a) or into the abdomen directly (b) will be obtained from the hospital supply. Thesyringes will be sterile at the time of use and will be operated so as to maintain sterility and patient safety.

7.2 Study Drug Dosage and Administration

The drug will be administered intra-abdominally at a dose of 1g/ Kg of subject body weight to the surgical sites, just prior to completion of the surgery. For laparoscopic surgery, the drug will be applied before expulsion of carbon dioxide gas and removal of instruments. For laparotomy surgery, the drug will be applied just before closure (suturing) of the abdominal incision. The treatment will be a single, or bolus dose at the end of surgery. The treatment will be evenly distributed over the operative site to ensure uniform results. The appearance and drug calculation of the placebo is the same as the study drug. Therefore the volume (i.e., number of vials) dosed, will correspond to the same volume (number of vials) used for the study drug.

The number of vials dosed per patient will be calculated based on her body weight.The group from which she is dosed will be dictated by the Randomization schedule for the block to which she has been assigned. As described in Section 7.1.1, Drug/Placebo, the study supplies will be supplied in packages of 2 or 3 vials each, labeled either Group A or Group B. The vials from Group A will be identical in

appearance to those in Group B, except for the label information. All vials will contain 20 mL of clear liquid.

As each patient is enrolled, her weight will be measured and the number of vials needed to provide 1g/Kg of drug (or an equivalent volume of placebo) will be determined. At the time of surgery, the surgeon will select from Group A or Group B the appropriate number of vial packs as dictated by the patient weight and the Randomization Schedule for her particular block.

For example, if the first block randomization is AABABB, and the first patient needs 7 vials of drug A based on her weight, then the surgeon will use 2 packets of 2 vials and one packet of 3 vials (total = 7) from Group A to dose the patient; 7 vials contains a total of 140 mL (20 mL per vial). For the next patient, he will dose from group "A" as well, and for the next 4 patients, from Groups B, A, B, and B respectively. Using this approach, the number of vials dosed may change from patient to patient, but the dose per Kg of body weight will be the same for each patient and the surgeon will not know if he is dosing drug or placebo at the time of surgery because the allocation of the drug/placebo in A vs B vials is blinded to the research team.

7.3 Drug Dose Modification

Drug dose modification is not considered necessary. L-Alanyl-L-Glutamine will be dosed by weight and administered on a one-time basis per subject.

7.4 Concomitant Treatment

No concomitant treatment or medication will be given as part of the study. Subjects will receive post-operative analgesia as prescribed by the attending physician.

No rescue medication is considered necessary.

Anti-inflammatory drugs or drugs with anti-inflammatory properties will not be allowed, however, Ibuprofen and other commonly used NSAIDS used for post-operative pain will be allowed.

Anti-epileptic drugs will not be allowed.

Nutritional supplements containing glutamine or alanine will not be allowed.

8. RISKS/PRECAUTIONS

L-Alanyl-L-Glutamine has no expected risks, side effects or toxicities. The adverse events and serious adverse events will be monitored. Evaluation, reporting and recording of adverse events can be found in Section 10.

9. STUDY PROCEDURES

9.1 Screening and Baseline Procedures

After signing the informed consent, prior to surgery the following data will be collected and study procedures will be performed. This may be done at the time of the diagnosis and decision for myomectomy, preoperative clinic or on the surgical day.

Body Mass:

- Height (M)
- Weight (Kg)

Vital Signs:

-Temperature

-Heart Rate

- Blood Pressure

Blood/Serum Tests:

-Full Blood Count

- Haemoglobin
- Haematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count
- White blood cell differential count
- Platelet count
- Liver enzymes: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and Alkaline Phosphatase (ALP)
- Kidney Function Tests: Blood Urea Nitrogen (BUN and Creatinine

Beta Human Chorionic Gonadotropin test

The Investigator will evaluate the subject's eligibility for randomization based upon the inclusion/exclusion criteria.

9.2 Treatment Procedures

The treatment will be a single dose of L-Alanyl-L-Glutamine (1g/kg of body weight) or placebo, which will occur at the time of surgery, just before closure of the surgical wound (refer to 7.1.1, 7.1.2 inthe laparoscopic or laparotomy myomectomy

SOP). Any excess blood or fluid will be removed from the abdomen prior to placement of the treatment drug or placebo to avoid dilution of the treatment drug. The treatment or placebo will be administered intraabdominally using a syringe attached to a catheter (laparoscopy) or intravenous blunt needle or cannula (laparotomy). The treatment or placebo will be evenly distributed over the myomectomy incision sites to ensure uniform dispersal. If any adhesions are present at the time of initial myomectomy surgery, incidence and severity of the adhesions will be assessed and graded using a AFS adhesion score. The surgeon will lift and reposition the ovaries, fallopian tubes and uterus to grade adhesions and to demonstrate for videotaping purposes, according to standard surgical care.The myomectomies will be completed by laparoscopy or laparotomy according to the standard medical care in Ukraine.

9.3 Follow-up Procedures

Each subject will be monitored according to the standards for in hospital post – operative care. Upon discharge from the hospital, subjects will receive follow-up care with their primary surgeon as needed. Subjects will be given a diary card, which will require them to make weekly entries and respond to a number of questions, including but not limited to quantity of pain medications used daily and pain scores using a 10 point pain analogue scale. Telephone follow-up with each subject will be conducted at 1, 4 and 7 weeks post surgery. The diary card will be submitted to the study investigator at the 6-8 week follow-up visit. *See Appendix 4 for an example of the diary card.* 7 to 9 days post-operation, the subject will be required to complete a blood test to evaluate liver enzymes through the community laboratory. This will be prompted at the week 1 telephone follow-up.

At 6-8 weeks post surgery and treatment, subjects will report back to the hospital for a second look laparoscopy to evaluate the efficacy of the treatment. Incidence and severity of the adhesions will be assessed and graded using an American Fertility Society adhesion score. A visual evaluation and adhesion score will be completed by the surgeon(s). The cine-loop and still images obtained from the 6-8 week follow up laparoscopic procedure will be used to record treatment effects. The videotapes will later be reviewed by independent study assessors who are blinded to the treatment allocation and to the time of videotaping (before myomectomy vs after myomectomy timeline)

Subjects will be followed from the time of hospital discharge until the eight-week follow up visit. The AdeTherapeutics' Study Investigator will conduct telephone check-ups at week 1, 4 and 7 post-operatively with each subject and record the subjects' comments in their CRF (Case Report Form). Questions regarding pain and quality of life following the initial surgery will be discussed. Subjects will be encouraged to identify and discuss any of their questions or concerns. The Principal Investigator will review the CRFs.

The following tests will be performed at the 6-8 week follow-up laparoscopic procedure:

Body Mass:

- Height (M)
- Weight (Kg)

Vital Signs:

-Temperature

-Heart Rate

- Blood Pressure

Blood/Serum Tests:

-Full Blood Count

- Haemoglobin
- Haematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count
- White blood cell differential count
- Platelet count

- Liver enzymes:

- Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and Alkaline Phosphatase (ALP)

- Kidney Function Tests: Blood Urea Nitrogen (BUN and Creatinine

Volume of blood necessary for each test will be according to the lab standards responsible for collecting the tests.

Safety Assessment:

- Adverse events, adverse drug reactions
- Physical examination, including weight & vital signs
- Clinical laboratory abnormalities

9.4 Schedule of Events

TABLE 1: Schedule of Assessments

Assessment	***Pre-Operative Assessment***	***Myomectomy***	***Post-Operative Care***	***6-8 Week Follow-up***
Informed Consent	*X*			
Inclusion/Exclusion Criteria	*X*			
Physical Exam	*X*	*X*	*X*	
Vital Signs	*X*	*X*	*X*	
Laboratory Assessments	*X*	*X*	*X*	
Pre-op Parameters	*X*	*X*		
Treatment Administration		*X*		
Surgery		*X*		*X*
Adhesion Assessment		*X*		*X*
Adverse Events		*X*	*X*	*X*

10. EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

Russlan Clinicals' Standard Operating Procedures will be followed with regard to the evaluation, recording, and reporting of adverse events.

All adverse events either observed by the Investigator or one of his medical collaborators, or reported by the subject spontaneously or in response to a direct question, will be noted in the adverse events section of the subject's Case Report Form (CRF) and source document.

If any adverse event is reported, the date of onset, relationship to study medication or treatment, any action taken, date of resolution (or the fact that it is still continuing or has become chronic), outcome, and grading of the adverse event serious, moderate or minor will be recorded. The different options for these categories are defined in Section 10.1.4.

The adverse event reporting period begins after the treatment has been delivered and ends at the completion of the 8-week follow-up assessment. The Investigator will

follow all adverse events until they have resolved or it is determined that they have become chronic.

10.1 Definitions

10.1.1 Adverse Event

As per International Conference for Harmonization (ICH) guidelines, an adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the administration, at any dose, of a medicinal or therapeutic product whether or not considered related to that product.

10.1.2 Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that (at any dose):

- **results in death.**
- is life-threatening (i.e. the patient was at risk of death at the time of the event).
- requires inpatient hospitalization of ≥ 24 hours or prolongs existing hospitalization.
- results in persistent or significant disability / incapacity.
- results in a congenital anomaly / birth defect.
- is medically significant and may jeopardize the subject or may require intervention to prevent one of the outcomes listed above Adverse Event Descriptors.

10.1.3 Intensity

The intensity of adverse events will be characterized according to ICH guidelines.

10.1.4 Relationship to Study Treatment

The causal relationship to study drug or treatment will be determined by the responsible Investigator according to best medical judgment, as follows:

None	The event is definitely not associated with the study drug or treatment.
Unlikely	The temporal association, subject history and/or circumstances are such that the study drug or treatment is not likely to have

Possible	The event follows a reasonable temporal sequence from study drug or treatment but could have been produced by the subject's
Probable	The event follows a reasonable temporal sequence from the study drug or treatment, abates upon discontinuation of the
Definite	The event follows a reasonable temporal sequence from the study drug or treatment, abates upon discontinuation, cannot be explained by known characteristics of the subject's clinical
Unknown	Events for which some information exists, but no firm evaluation of relationship to study drug or treatment can be

10.1.5 Additional Reporting Guidelines

Adverse events include the following:

- Events arising from overdose, abuse, withdrawal, sensitivity or toxicity.
- Apparently unrelated illnesses, including worsening of a preexisting illness. A preexisting illness is defined as a disorder present before the adverse event reporting period starts and is noted as such on the pretreatment medical history, physical examination, or baseline signs and symptoms Case Report Form page. Any worsening of the condition, including an increase in frequency, will be reported as an adverse event.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (e.g. a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as two separate events. The outcome of the accident (e.g. hip fracture secondary to fall) should be recorded as part of the event description, but not as a separate event.
- Abnormalities in physiological testing or physical examination. These are usually only reported as adverse events when the finding requires intervention or investigation beyond a repeat confirmatory test. For any change in, for example, vital signs or electrocardiogram measurements that arise after treatment, the Investigator will decide if the value is clinically significant. If so, the evaluation should be repeated. If the result is still clinically significant after being repeated, the abnormality must be recorded as an adverse event.
- Laboratory abnormalities requiring clinical intervention or further investigation beyond a repeat confirmatory test, unless associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g. elevated liver enzymes in a patient with jaundice) should be described as part of the clinical event and not as a separate adverse event.

Laboratory values that are outside of normal limits should be repeated as appropriate. Treatment-emergent laboratory abnormalities that the Investigator determines are clinically significant and/or require treatment or a change in the subject's treatment will be recorded as an adverse event.

- Diagnostic and therapeutic non-invasive and invasive procedures such as surgery should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event (e.g. an acute appendicitis is considered to be an adverse event, and the resulting appendectomy is the action taken).
- Symptoms of baseline disease will be captured on the adverse event pages of the subject's Case Report Form along with their intensity. A worsening of baseline symptoms will result in a new entry on the Case Report Form.

10.2 Reporting and Evaluation of Serious Adverse Events and Other Clinically Significant Adverse Events

The investigator will ensure that adverse event data is collected from primary care physicians and subjects between the 6-8 weeks after being discharged from the hospital to follow-up assessment by:

- Keeping detailed and accurate records of each subject's primary care physician.
- Communicating with each subject's primary care physician at least once per week following discharge of the subject from the hospital, to obtain data regarding any incidents occurring during treatment/visits/consultation with the subject during the 8- week period prior to the follow-up assessment visit to the clinic.
- Documenting thoroughly, as per GCP requirements, all reports from physicians.
- Documenting thoroughly any reports received directly from subjects.
- Ensuring that serious, unexpected adverse events that arise during the twenty-four hour post surgical hospital stay, or those reported to subjects primary care physicians, or those reported directly to the Monitor are handled as per current regulatory requirement as follows:

1. Where Adverse Drug Reaction is neither fatal nor life threatening, within 15 days after becoming aware of the information.
2. Where it is fatal or non-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information.
3. Within 8 days after having informed Health Canada of the ADR, AdeTherapeutics will submit a report, which includes an assessment of the importance and implication of any findings.
4. Each ADR which is subject to expedited reporting should be reported individually in accordance with the Health Canada/ICH Guidance Document E2A: Clinical Safety Data Management: Definitions and Standards for Expediting Reporting.

11. STUDY VARIABLES AND STATISTICAL ANALYSIS

The study will be analyzed using the intention-to-treat approach. Both the subjects and investigators will remain blinded to the study code until the final analyses.

11.1 Sample Size/Power Considerations

Although this study is essentially a Phase I study, randomization and blinding have been incorporated into the experimental design to ensure the validity of any conclusions made regarding the tolerability of the AdeTherapeutics' formulation in peritoneal tissues as well as proof of concept for L-Alanyl-L-Glutamine in the proposed

application. The study has been appropriately powered to rule out false acceptance or rejection of the null hypothesis, so that sound decisions can be made as to whether or not to move forward with further studies that will, by nature, involve surgical patients.

Assuming 80% with no adhesions in the treatment group compared to 10% with no adhesions in the placebo group at six to eight weeks post surgery, 13 evaluable subjects per group would be needed to demonstrate statistical difference to achieve 90% power at the 0.05 significancelevel. The calculation is based on Fisher's Exact test. Adjusting for 10% attrition (including lost to follow-up) a total of 48 subjects will be needed in the study: 38 subjects will be recruited to the laparoscopic group (19 subjects to receive treatment, 19 subjects to receive placebo), 10 extra subjects will be recruited to undergo myomectomy by laparotomy. This does not affect the study's power. The recruitment does ensure that the most adhesiogenic surgical procedures will be represented.

11.2 Data Sets To Be Analyzed

11.2.1 Efficacy

The study will be analyzed using the intention-to-treat approach. Both the subject and the investigators will remain blinded to the study code until the final analyses.

(a) Incidence of adhesions:

The number and the proportions of adhesions will be compared using chi-square or Fisher's exact test. (Altman, 1997). The odds ratio with 95% confidence intervals will

be calculated during Cochran-Mantel-Hanzel method. Univariate and Multivariate logistic regression models for incidence will be performed (Homer, 1989).

(b) Severity of adhesions:

At the time of surgery, each patient's existing adhesions will be scored based on the American Fertility Society scoring system, as follows: (Stage A- minimal adhesion score 0-5, Stage B- mild adhesion score 6-10, Stage C- moderate adhesion score 11-20, Stage D- severe adhesions score 21-32). The patient will be scored again at the 6-8 week follow up and the difference between the two scores will be determined and used as the patient's actual score in the statistical analyses. The panel of experts scoring adhesions at each time point will be blinded as to the time point and the treatment group (i.e. L-Alanyl-L-Glutamine or Placebo). This approach will ensure that there is no bias in the patient's adhesions scoring.

The patients' actual score will be re-categorized as nonadhesion (Stage A and B) and adhesion (Stage C and D) and use chi-square or Fisher's Exact test to determine the differences in adhesion severity between the two study groups. The odds ratio with 95% confidence intervals will be calculated using the Cochran-Mantel-Hanzel method. A logistic regression model for severity of adhesion could also be considered, if feasible. Any differences with a $P< 0.05$ will be considered statistically significant. The analysis will be performed using the SAS statistical package (SAS, version 9, SAS Institute, Cary, NC).

11.2.2 Safety

The number of adverse events and adverse drug reactions will be analyzed by chi-square test or Fisher's Exact test to determine any differences between two study groups.

11.3 Analysis of Demographic and Baseline Data

Initial descriptive analyses will be done. For continuous variables, a student's t-test or the Wilcoxon rank sum test will be used. For categorical variables, chi-square or Fisher's Exact test will be used.

11.4 Efficacy Variables and Analyses

Descriptive analyses will be done. Distribution of continuous variables will be examined for normality to determine whether to use parametric or non-parametric statistics. If the distributions are not normal, appropriate transformation will be used to normalize them. A student's t-test or the Wilcocon rank sum test will be used for continuous variables. A chi-square or Fisher's Exact test will be used for categorical variables.

11.5 Safety Variables and Analyses

Adverse events, adverse drug reactions and clinical laboratory abnormalities will be analyzed by using the chi-square test or Fisher's Exact test. Any continuous measurement in physical examination and clinical laboratory will be analyzed by t-test or Wilcoxon rank test.

11.6 Interim Analysis

There will be no interim analysis.

12. ESTIMATED DURATION OF THE STUDY

The duration of the study will be approximately twelve (12) months from first patient in to last patient out. The duration for each subject will be 6-8 weeks, from the time of the myomectomy to the second-look laparoscopic assessment.

13. STUDY ETHICAL CONSIDERATIONS

13.1 Ethical Conduct of the Study

The study will comply with the Declaration of Helsinki, ICH "Guideline for Good Clinical Practice", World Health Organization recommendations and any other applicable regulatory requirements. AdeTherapeutics will ensure that the study complies with all local, provincial or country-specific regulatory requirements as applicable.

13.2 Informed Consent

The informed consent forms used for the study will comply with GCP and other regulatory requirements. It will be approved by the Sponsor (prior to review by the Institutional Review Board [IRB]/ Ethics Committee [EC]) and the Investigator's IRB. A sample informed consent form is provided in Appendix 3. The Investigator or an authorized associate, who will be a physician, will explain orally and in writing the nature of the study and the treatment in such a manner that the subject is aware of potential benefits and risks. Subjects will also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Documentation of the discussion and the date of informed consent will be recorded in the source documentation. Subjects will be required to give informed consent in writing.

13.3 Institutional Review Board or Ethics Committee

The protocol, any protocol amendments and consent form for the proposed clinical study and any other documents required by the local Institutional Review Board (IRB) or Ethics Committee (EC) will be submitted by the Investigator for review and approval. The Investigator will also ensure that the IRB/EC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of the approval letter will be forwarded to the Sponsor before the study is implemented.

14. ADMINISTRATIVE PROCEDURES

14.1 Sponsor's Responsibilities

14.1.1 Study Supplies

AdeTherapeutics is responsible for providing the study drug (L-Alanyl-L-Glutamine) and storage space for data.

14.1.2 Investigator Training

The Principle Investigator(s)and their study personnel will receive training regarding the study procedures. This training will take place prior to enrollment of the first subject at each study center. The study center will be provided with information

regarding Good Clinical Practices and regulations specific to the conduct of clinical trials. Training will be provided by Numoda.

14.1.3 Study Monitoring

A qualified Study Monitor, appointed by AdeTherapeutics will monitor the study. The monitor will be a representative of AdeTherapeutics. Routine monitoring visits will be conducted to:

- Assure compliance with the study protocol.
- Review the subjects' CRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
- Ensure that adequate records of clinical trial supplies are maintained.
- Verify that the Investigator and study site personnel are adequately qualified throughout the study.
- Verify that the research facilities, including laboratories and equipment, are adequate to safely and properly conduct the study.
- Verify that the investigational product[s] are stored properly and under the proper conditions, are in sufficient supply, and that receipt, use, and return of investigational product[s] at the study sites are controlled and documented adequately.
- Verify that written informed consent was obtained before initiation of any screening procedures that are performed solely for the purpose of determining eligibility for the clinical study and/or prior to the provision of study medication.
- Verify that the safety information and amendments are submitted to the IRBs.
- Results/findings of all monitoring visits will be appropriately recorded.

14.2 Investigator's Responsibilities

14.2.1 Reporting and Recording of Study Data

All requested study data must be recorded legibly on the Case Report Forms (CRFs) provided for the study. An explanation should be provided for all missing data. Correction of data on the CRF will be made by crossing out the incorrect entry with a single stroke and entering the correct data beside it with the initials of the individual making the correction and date of the correction. Only individuals who are identified on the Authorized Signature Page may correct data in the CRF. For those subjects who withdraw before completion of their specified treatment regimen, all available efficacy and safety data must be entered in the CRF. If provided by the subject, the reason for withdrawal will be included in the CRF. Incomplete or inconsistent data on the CRFs will result in data queries that will be returned to the Investigator for resolution.

14.2.2 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which case reports for each subject are based. They are to be separate and distinct from CRFs, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the subject's CRF is appropriate. Source documents will be maintained according to Ukrainian law.

14.2.3 Study Drugs

The Investigator is responsible for ensuring the study drugs are administered or dispensed only to subjects enrolled in the study. An accurate accounting of the study drugs must be maintained using a separate form (Accountability Record Forms). These records must show dates, lot numbers, quantities received and dispensed. The Investigator will return any unused study drug and other study material to the Sponsor at the completion of the study.

14.2.4 Records Retention

The Investigator must arrange for the retention of all study documentation (such as CRFs, research files, and master files) for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. The Sponsor must retain all other documentation pertaining to the study for the lifetime of the product. Archived data may be held on microfiche or electronic record, provided that a back-up copy exists and that a hard copy can be generated if required.

The Investigator must inform the Sponsor immediately if any documents are to be destroyed, to be transferred to a different facility, or to be transferred to a different owner.

15. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

Sponsor encourages the scientific publication of data from clinical research trials. However, Investigators may not present or publish partial or complete study results individually. The Principal Investigators and the Sponsor may propose appropriate scientific manuscripts or abstracts from the study data. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by the Sponsor before submission for publication. Names of all investigators participating in the study will be included in the publication.

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17. APPENDICES

APPENDIX 1. Investigator Signature Page

APPENDIX 2. Drug Infusion and Constitution Procedures

APPENDIX 3. Sample Informed Consent Form

APPENDIX 4. Sample Diary Card

APPENDIX 1

Investigator Signature Page

Protocol Number:	Ade002-2013
Title of Protocol:	A Proof of Concept Study of the Efficacy and Safety of L-Alanyl-L-Glutamine for the Reduction of Peritoneal Adhesions in Adult Females Undergoing a Myomectomy
Date of the Protocol:	19/08/2013

AGREEMENT

This document is a confidential communication of AdeTherapeutics. The recipient agrees that no unpublished information contained herein will be published or disclosed without the prior written approval of AdeTherapeutics. However, this document may be disclosed to appropriate Institutional Review Boards, Ethics Committees, or authorized representatives of the Investigator or of Boards of Health under the condition that they are requested to respect the confidentiality of the document.

The signature of the Investigator below constitutes his/her agreement to comply with the contents of this protocol.

Donna Chizen, MD

INVESTIGATOR'S NAME AND TITLE

INVESTIGATOR'S SIGNATURE

DATE

APPENDIX 2

Drug Infusion and Constitution Procedures

1. Drug & placebo are stored in 20ml vials containing 20mls of drug or placebo.
2. The concentration of the drug is 400mg/ml.
3. The subject's dose will be determined based on their body weight in kilograms.
4. The dose will be drawn up from the vial into a sterile syringe maintaining sterility.
5. The syringe is attached to the luer lock adapter.
6. The luer lock adapter is attached to the 16 FR drug delivery system (catheter, blunt needle or plastic intravenous cannula)

APPENDIX 3

Informed Consent Form

A Proof of Concept Study of L-Alanyl-L-Glutamine For the Reduction of Peritoneal Adhesions in Adult Females Undergoing Myomectomy

Research Participation Information Sheet

Research Participation Information Sheet

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Funder: AdeTherapeutics, Inc

You are invited to participate in this study because you have uterine fibroids and will be undergoing a surgery to remove the fibroids. Fibroids are also called uterine myomas and the surgery to remove a fibroid is called a myomectomy. You are considering volunteering in a research study that is conducted by the Women's Health Imaging Research Laboratory in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of Saskatchewan, Saskatoon, Canada. Before you give your consent to be a research participant, please read this information sheet and ask as many questions as necessary to be sure that you understand what your participation will involve. Your participation is entirely voluntary, so it is up to you to decide whether or not to take part in this study. If you do decide to take part in this study, you arefree to withdraw at anytime without giving any reason for your decision nor will you lose the benefit of any medical health care to which you are entitled or are presently receiving.

This research will be conducted at the Women's Health Imaging Research Laboratory in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of Saskatchewan. The study site will be through the Department of Obstetrics and Gynecology at the Royal University Hospital and Saskatoon City Hospital in Saskatoon, Saskatchewan.

The Funder of this study, AdeTherapeutics, will reimburse your doctor and the clinic hospital for the costs of undertaking this study. However, neither the institution nor any of the investigators or staff will receive any direct financial benefit from conducting this study. The study may lead to the development of commercial products. There are no

plans to share with you any financial profits resulting from the use of your samples or data.

Purpose of the study:

Adhesions are abnormal deposits of fibrous scar tissue that can form within the abdomen. Inflammation and adhesions form as the body attempts to repair itself after inflammation, infection or injury. Abdominal adhesions around the reproductive organs are common causes of pelvic pain and infertility. Up to 97% of gynecological surgeries can result in adhesion formation.

Currently, there is no standard of care to prevent post-operative adhesions. Various methods of adhesion prevention and treatment have been tried but they have had limited success. The purpose of the present study is to characterize the adhesion reduction effect of L-Alanyl-L-Glutamine after pelvic surgery. Glutamine is an essential amino acid that the body is unable to make on its own in sufficient quantity under circumstances such as surgery. The study drug, which is compromised of L-Alanyl-L-Glutamine is safe and well absorbed in the body. Many people currently take it orally or by injection as a nutritional supplement. However, L-Alanyl-L-Glutamine has not yet been examined in humans to prevent adhesions. We have performed preliminary studies in animals that demonstrate that it is very effective in reducing adhesion formation following surgery. On the basis of these trials, we expect that the compound will significantly reduce the number and severity of adhesions following human surgical procedures.

Procedures:

Approximately 40 women who have been diagnosed with uterine fibroids and meet all the necessary requirements for entry into the study will be asked to participate. If you are selected and choose to participate, your total participation time will be approximately eight (8) weeks. Once you have signed the consent form you will be randomly assigned to either the treatment group or the placebo group. Random assignment is an experimental technique used to divide research participants into treatment and non-treatment groups without creating bias. A placebo is a substance that looks like and is given exactly like the drug, but contains no active medical ingredients. The study is double-blinded which means that the investigator, principal investigator, surgeon and any other hospital staff involved in your care do not know what group you are assigned to. In the event of a medical emergency, the blind can be broken to ensure proper medical care and safety.

The surgery procedure that you will undergo is a myomectomy, which is a standard surgical procedure for the removal of uterine fibroids. The location of the fibroids will be determined and removed, as per normal procedures. For study purposes, before the surgery is finished, your surgeon will apply either the treatment drug (L-Alanyl-L-Glutamine) or the placebo to the area. During the surgery, digital video and photographs will be taken of the affected area for the study and stored in our study files. You will be admitted to a surgical ward for standard post-operative monitoring and care. In

conjunction with the study, you will receive any and all standard follow-up care that your surgeon requires. (See Saskatoon Health Region's Surgical Check-List attached)

Upon discharge from the hospital, you will be given a diary card with a number a questions. You will be required to answer these questions at the end of each week for eight (8) weeks. The investigator will conduct telephone check-up interviews 1, 4 and 7 weeks after your surgery. These interviews will consist of a few questions related to your diary card and any pain or symptoms you may be feeling post-operatively. For study purposes, on week 6-8 you will be required to report back to the hospital for a follow-up second-look laparoscopic procedure. During the follow-up surgery, digital video and photographs will be taken of the your reproductive organs. Any adhesions that are present will be assessed, photographed and removed. These follow-up conversations, tests and surgery allow the research team to ensure that you are receiving the highest quality of care.

Schedule of Assessments

Assessment	***Pre-operative Assessment***	***Myomectomy***	***Post-Operative Care***	***6-8 Week Follow-up***
Informed Consent	*X*			
Inclusion/Exclusion Criteria	*X*			
Physical Exam	*X*	*X*	*X*	
Vital Signs	*X*	*X*	*X*	
Laboratory Assessments	*X*	*X*	*X*	
Pre-op Parameters	*X*	*X*		
Treatment		*X*		

Administration				
Surgery		*X*		*X*
Adhesion Assessment		*X*		*X*
Adverse Events		*X*	*X*	*X*

You will be asked to sign 2 copies of the Research Participant Information Sheet and attached Consent Form after having thoroughly read and reflected on them before initiating any study procedures. A witness may be present when you sign the Consent Form. One copy of the information sheet and consent form will be retained in our study files and one copy will be given to you for your records.

Research Related Injury Statement:

In the event that you become ill or injured as a result of participating in this study, necessary medical treatment will be made available at no additional cost to you. By signing this document you do not waive any of your legal rights. In case of a medical emergency, you should seek immediate care, and as soon as possible, notify the study doctor.

Foreseeable Risks and Discomforts:

There are no expected side effects associated with L-Alanyl-L-Glutamine.

The use of the treatment drug or the placebo should not pose any risks or discomforts.

The risks of the myomectomy surgery may include bleeding, trauma and infection, will be discussed with you by your surgeon prior to your surgery. Your surgeon will discuss the method for removing fibroids (myomectomy) by either laparoscopy or by laparotomy that is the preferred method to provide you with the best care. No additional surgical risks are anticipated as a result of participating in the study.

The 6-8 week follow-up laparoscopic surgery is a necessity of the study. It is important to see if any scar tissue has formed after receiving the study drug or placebo. The risks of a second laparoscopy are similar and may include bleeding, trauma and infection, and will again be discussed with you by your surgeon.

Benefits of the Study:

You may benefit from the follow-up surgery because scar tissue around the uterus, fallopian tubes, bowel and belly wall can be removed if present. During the study, we may see that women who received the study drug during surgery have less scar tissue than women who received the placebo.

It is hoped the information gained from this study can be used in the future to benefit other people with a similar condition. If you choose to participate in this study, there may or may not be any direct benefit to you.

Compensation:

You will not be charged for the study drug(s) or any research-related procedures. You will not be paid for participating in this study. An honorarium of $250.00 will be provided to cover your time and out-of-pocket expenses such as travel, parking or meals. If you decide to withdraw early from this study, your compensation will be proportional to your time in the study. Because this honorarium is over $50.00 your Social Insurance Number (SIN) will be forwarded to financial services at the University of Saskatchewan for taxation audit purposes.

Confidentiality:

In Saskatchewan, the Health Information Protection Act (HIPA) protects the privacy of your personal health information. Your privacy will be respected.

Your study records will be identified bya number assigned to you at the beginning of the study. They will be kept for 20 years in a secure area such as a locked file cabinet. Results of the study without your name or other information that could identify you will be combined with information from other participants for analysis.

No information that discloses your identity will be released or published without your specific consent. Some authorities have a duty to check your study and medical records to make sure all the information is correct. Your study and medical records may be inspected in the presence of the investigator or his/her qualified designate by representatives of Health Canada or the University of Saskatchewan Research Ethics Board.

If you decide to withdraw from this study, your study and medical records will be made available to these agencies. However, they will only look at your records up to the date of your withdrawal, except where the reporting of side effects associated with the study medication is required. Rarely, your study documents may be obtained by courts of law. You may ask the study doctor to see and copy your personal health information related to the study. You may also ask the study doctor to correct any study related information about you that is wrong. In the case of a blinded study, you may have to wait until the end of the study to see your study records to protect the integrity of the study.

The results of this study may be presented in a scientific meeting or published, but your identity will not be disclosed.

For your own safety, it is strongly recommended that your family physician be informed of your participation in this study. With your permission, he/she will be informed and may be consulted regarding your health and treatment.

Alternatives to Participation in this Study:

You do not have to participate in this study to receive treatment for your condition. If you choose not to participate in this study, you will still receive standard of care treatment for your uterine fibroids. Your study doctor will discuss the options with you, including the risks and benefits of each option.

Voluntary Participation/Withdraw from the Study:

Your participation in this study is purely voluntary. You may decide not to participate or may withdraw at any time. Your refusal to participate in, or your withdrawal from, the study will not affect your medical care in any way. If you wish to withdraw from the study, please notify any member of the Research Team as soon as possible and the appropriate arrangements will be made.

Your participation in this study may be ended at any time, without your consent. Reasons may include, but are not limited to, your failure to follow study instructions, the appearance of side effects, or study cancellation due to administrative reasons.

The blinded nature of this study does not allow for information about the study to be revealed until the entire study is completed. Once the study has been completed, it is

possible for you to receive the results of the study. If you are interested in understanding and learning about the results, please ask the study coordinator for this information.

Questions Regarding Participation:

If you have any questions regarding your participation in this study, please feel free to call:

Principal Investigator: Dr. Donna R. Chizen, MD

Tel: (306) 966-8623

Fax: (306) 966-2981

Study Coordinator: Dominique Singh, BSN, RN

Tel: (306) 292-7756

Fax: (306) 966-8796

If you have any questions about your rights as a participant or concerns about the study, you should contact the Chair of the Biomedical Research Ethics Board, c/o the Ethics Office, University of Saskatchewan at 966-4053.

Consent Form

I have read and understand the attached Research Participant Information Package, and I freely and voluntarily agree to take part in the study entitled ***A Proof of Concept Study of L-Alanyl-L-Glutamine For the Reduction of Peritoneal Adhesions in Adult Females Undergoing Myomectomy.***

I have been given a copy of the Research Participation Information Package and will be given a copy of the signed and dated Consent Form. I have received an explanation of the purpose and duration of the trial, and I am aware of the potential benefits and side effects associated with the procedures involved in this study.

I was given sufficient time and opportunity to ask questions, to reflect on my understanding of and participation in the study. My questions have been answered to my satisfaction.

I agree to cooperate fully with the study personnel and will tell him/her of any medicine, drug or alternative therapy (herbal remedy) of whatever nature I have taken in the recent past, or am taking now, whether prescribed or not.

I understand that I am free to withdraw from the study at anytime, for any reason, and this will not affect my future medical treatment.

Please check the appropriate box to indicate your decision:

_____ Yes, I agree that the research study staff may inform my family doctor of my participation in this study.

_____ No, I do not want you to inform my family doctor of my participation in this study.

_____ _____

Signature of Participant Date

Printed name of above: _____

I confirm that I have explained the purpose and procedures of this study, as well as any potential risks and benefits, to the participant whose name and signature appears above.

_____ _____

Signature Date

Printed name of above: _____

Study Role: _____ Initials: _____

Health Canada Santé Canada

GUIDANCE FOR INDUSTRY

Good Clinical Practice: Consolidated Guideline

ICH Topic E6

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Health Products and Food Branch
Guidance Document

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FOREWORD

This guidance has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and USA.

In adopting this ICH guidance, Health Canada endorses the principles and practices described therein. This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

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INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP guidance document is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guidance document was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guidance document should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guidance document may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

1. GLOSSARY

1.1 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

1.2 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

1.3 Amendment (to the protocol)

See Protocol Amendment.

1.4 Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

1.9 Audit Trail

Documentation that allows reconstruction of the course of events.

1.10 Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12 Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guidance for *Structure and Content of Clinical Study Reports*).

1.14 Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15 Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16 Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19 Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20 Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24 Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the

Independent Ethics Committee to act in agreement with GCP as described in this guidance document.

1.28 Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29 Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35 Investigator / Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36 Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure)

1.37 Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39 Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

1.40 Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41 Nonclinical Study

Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record

See Source Documents.

1.44 Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guidance the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

1.46 Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47 Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP guidance the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

  (see the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53 Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55 Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57 Subject/Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59 Trial Site

The location(s) where trial-related activities are actually conducted.

1.60 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

1.61 Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents: trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates
that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval/negative opinion; and
- termination/suspension of any prior approval/favourable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6 When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 Composition, Functions and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have
the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a nonscientific area.

(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the

subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.

(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume
responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician

and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely
from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change of, the protocol to
eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the
investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is
designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s)

are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the
applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to
subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject

or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any
other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may
refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e., a trial in which

there is no
anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies

should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 The investigator should submit written summaries of the trial status

to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC
(see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor,
the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly
inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see
3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and
quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure
direct access (see 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties
involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and

functions to a
CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guidance document also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guidance for *Structure and Content of Clinical Study Reports*, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5 Trial Management, Data Handling, and Record Keeping

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to
the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

(b) Maintains SOPs for using these systems.

(c) Ensure that the systems are designed to permit data changes in such a way that
the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific
essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with
the applicable regulatory requirement(s) of the country(ies) where

the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e.,
for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor-specific essential documents should be retained until at least 2 years after
the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6 Investigator Selection

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

(a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);

(b) to comply with procedures for data recording/reporting;

(c) to permit monitoring, auditing and inspection (see 4.1.4) and

(d) to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 Allocation of Responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related responsibilities.

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s))to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 Confirmation of Review by IRB/IEC

5.11.1 The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect
of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of
any IRB/IEC re-approvals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

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5.12 Information on Investigational Product(s)

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator

product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

(a) Ensure timely delivery of investigational product(s) to the investigator(s).

(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).

(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).

(d) Maintain a system for the position of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

(a) Take steps to ensure that the investigational product(s) are stable

over the period of use.

(b) Maintain sufficient quantities of the investigational product(s) used in the trials to

reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits,

samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement
that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access
to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 Safety Information

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the
regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17 Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institution(s),
to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s)
and with the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety

updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 Monitoring

5.18.1 Purpose

The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central

monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4 Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

  (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

  (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

  (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

  (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

  (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the
specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enrolling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

(ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

(iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 Monitoring Report

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed

and the
monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 Selection and Qualification of Auditors

(a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guidance for *Structure and Content of Clinical Study*

Reports. (NOTE: The ICH Guidance for *Structure and Content of Clinical Study Reports* specifies that abbreviated study reports may be acceptable in certain cases.)

Preparing a Consent Form

The consent form is one aspect of a process to inform a potential research participant so that he/she can make a decision about participation in a study. Consent begins when a potential participant is first informed of the existence of a study and ends some time after its conclusion. The consent form is an important part of this process.

The consent form has the following objectives:

- It is an **information tool**. In theory, it is read carefully by a potential research participant before agreeing to participate. It is not a substitute for good communication between the researcher and a potential participant.
- It is a **reference document** that allows a research participant to follow the progress of a study step be step. As such, the consent form promotes adherence and retention in that a research participant does not have to remember everything and is less likely to get confused.
- It reminds the research participant of relevant **legal rights**.
- It is a **source of information for the researchers** in outlining all of the information that must be communicated to a potential research participant and how to communicate that information.

There are four essential elements in a consent form:

4. The voluntary nature of participation and the right to withdraw from a study at any time are the cornerstones of the consent process and must be stated unequivocally.
5. There must be a clear and understandable description of the purpose of the study and of all the procedures so that a potential research participant is informed of the extent of his/her involvement at each step of the study.
6. There must be a comprehensive description of the benefits and risks associated with the study.
7. There must be an indication of how the researcher intends to safeguard the anonymity of the participant and the confidentiality of the information collected.

The following document provides a step by step description of each element of a consent form and why it is required in some studies. **It is intended as a guide only. Not all elements are necessary or required for each study. The consent form must be appropriate in length and content to the characteristics of each study.** The consent form must address the potential research participant directly ("You are invited …") with language appropriate to the age and reading level of the intended participant. The style must be simple, avoiding or explaining in lay terms scientific or medical words or expressions. Legalistic phrases or expressions are also to be avoided so the consent form does not read like a contract.

Suggested wording for each section is provided in text boxes. Researchers are free to cut and paste keeping in mind the text should be adapted to the specificity of the study.

[Institutional logo/letterhead]
PARTICIPANT INFORMATION AND CONSENT FORM

The heading "Participant Information and Consent Form" should specify, if necessary, to whom it is directed (participant, control, parent, sibling, etc.).

Title of Study

- Should convey that the proposed intervention is for research rather than for educational, treatment, or other purposes.

7.3.5 Must be the exact title of the research protocol. A short, simplified title may accompany the title if it is too difficult for a layperson to understand.

2. If more than one consent form is required, each consent form should be titled appropriately (e.g., consent forms for tissue/blood banking, pharmacokinetic studies).

Principal Investigator

- Name, Institution and Contact Information

Sub-Investigator(s)

- Name and Institution

Sub-investigators may not need to be listed if they have little or no contact with study participants (e.g. for referrals, or doing laboratory tests).

Student(s) Researchers

1.2 If the researcher is a student, this must be explicitly stated and the supervisor clearly identified.

Sponsor

- Name(s) of industry sponsor or granting agency (as applicable)

Emergency Telephone Number

1.3 A 24-hour, 7-day a week phone number is required for studies that are more than minimal risks to research participants from participation.

INTRODUCTION

The introduction is required for all studies. It is the invitation to participate. The reason to invite these particular individuals should be stated by describing characteristics of the sample population that are important for the study. The introduction also stresses the voluntary nature of participation and the right to withdraw at any time.

Suggested Wording

You are invited to take part in this research study because you ……

Your participation is voluntary. It is up to you to decide whether or not you wish to take part. If you decide to participate, you are still free to withdraw at any time and without giving any reasons for your decision. If you do not wish to participate, you will not affect your {care, employment or academic standing, as applicable}.

Please take time to read the following information carefully. You can ask the study doctor or staff to explain any information that you do not clearly understand. You may ask as many questions as you need. Please feel free to discuss this with your family, friends or family physician before you decide.

WHO IS CONDUCTING THE STUDY?

This section is required for all studies. It is used to name all agencies contributing funds {including grants-in-aid}, resources, drugs, and other products to the study.

This section is also used to declare any other actual or potential conflicts of interest for conducting or being involved with any part of the study. For instance, the possibility of

commercialization of research findings that may benefit the local institution and / or researchers should be mentioned, when applicable.

Suggested wording
Scenario #1

The study is being conducted/sponsored by the [name of research group, e.g., Industry sponsor/Granting agency].The [study doctor, and institutions, as applicable] are being paid to conduct this research study.

Scenario #2

The sponsor of this study [name] will reimburse [study doctor and the institution] for the costs of undertaking this study. However, neither the institution nor any of the investigators or staff will receive any direct financial benefit from conducting this study.

WHY IS THIS STUDY BEING DONE?

This section is required for all studies. It provides a brief explanation why the research is being done. A participant should understand clearly why a particular health problem/intervention needs to be studied. For example, this can include non-technical information on the incidence of a disease, on the problems associated with a disease, on the poor outcomes for other treatment methods, etc. It should indicate if the study is "observational" (e.g. collection of clinical data or other information in a unique population) or "experimental" (how does it differ from standard care – e.g. new drug, dietary or herbal supplement, new formulation of an approved drug, different doses than commonly used, new device, new order of treatments for a particular condition, as applicable).

Key points to include in this section, when applicable:

1.4 clearly explain what the standard treatment(s) is/are and what basis exists for the experimental intervention;

1.5 indicate if the research is being carried out for the first time in humans;

1.6 indicate if the research is part of a larger multi-site clinical trial;

1.7 indicate the number of participants to be recruited at the local site.

Suggested wording

This study is being done because … *{add brief explanation of the research question }*.

WHO CAN PARTICIPATE IN THE STUDY?

This section is not required in most studies. It is used to specify the inclusion and exclusion criteria for the study. **It is the investigator's responsibility (and <u>not</u> the research participant's) to ensure that research participants fit the inclusion and exclusion criteria for research studies.** However, exclusion criteria which participants are likely to recognize (e.g. allergies, exposure to infectious conditions) can be listed, using lay terms (i.e., do not use diagnostic classes or technical language) if they provide an additional safeguard to participants from being inappropriately enrolled in research where they have personal health-related information, which may not be available to the investigators, and which could pose a significant risk or mitigate possible benefits from participation.

Suggested wording
You are eligible to participate in this study if …. *{add a brief description of the exclusion and inclusion criteria}*
Or
You should not/may not participate in this study if ….*{add a brief description of the exclusion criteria}*

WHAT DOES THE STUDY INVOLVE?

This section is required for all studies. The first paragraph is used to describe briefly in lay language the overall design of the study. This paragraph should include some or all of the following information, as applicable:

1.5 Indicate any specific tests required to determine eligibility (e.g. biopsy results, psychological tests, blood, tissue or urine analysis).

1.6 Describe the study groups and how participants will be assigned to the study groups (e.g. "You will be assigned randomly by a computer to group A or B").

1.7 If the study is "double-blinded", explain that neither the research participant nor the study doctor will know which treatment the research participant is receiving, but that information will be made available in the event of a medical emergency.

1.8 Indicate the time requirement for each study visits.

1.9 Indicate if study participation involves withholding of standard treatment before (wash-out period) and/or during the study. Provide justification to the research participant for the withholding of standard treatment. Indicate availability of "rescue medication", as applicable.

1.10 Indicate if the study includes a placebo arm. Please note that Article 7.4 of the TCPS indicates that the use of placebo controls in clinical trials is generally unacceptable when standard therapies or interventions are available for a particular patient population. For more details of circumstances in which a placebo may be used in a clinical study, consult the TCPS, section 7.4. If the test article is compared to placebo, the consent form must inform the potential participant about:

- any therapy that may be withheld or withdrawn for the purposes of the study;
- the possible consequences of withholding or withdrawing this therapy;
- the reasons why the use of the placebo is considered necessary;
- the chance of being assigned to the placebo arm of the study;
- the availability of "rescue medication",
- the right to withdraw should the research participant feel his/her condition is worsening.

The **next paragraphs** must describe **ALL** research-related procedures including those that may be required before the experimental intervention is initiated. The explanations should be such that participants will be able to comprehend the extent of their involvement in the research study, as well as be able to understand each step of their participation. **In particular, the experimental procedures that are beyond standard care should be clearly laid out.** These may include standard or common investigations, which would not normally be done in routine clinical care for the particular problem being investigated, or which are done more frequently during the research than in routine clinical care for that particular problem.

It is often useful to divide the study in its various phases such as:

i) Initial Visit/Before You Begin the Study/Screening Visit
ii) Randomization Visit

iii) Study Visits - These can be described in a variety of ways depending on the research procedures (e.g., Day 1, 2, 3; During the First Year of Your Participation in the Study, During the Remaining Years of Participation in the Study; First/Second/Third Visit; For Participants in Group 1/Group 2).

iv) Expected Follow-up - Describe the number of follow-up visits and their duration.

Blood/Tissue collection

If blood, body fluids and tissue samples are collected, the consent form must include all of the requirements of TCPS 10.2.The consent form must indicate what will be done with these samples as part of the study and with any remaining samples upon completion of the study.

If blood testing is involved, indicate the amount of blood to be taken in mL, followed by lay terms (e.g. "teaspoons (≈5mL) or tablespoons (≈15mL), or equivalent to a standard blood donation") and the purpose of the blood sampling.

Mandatory tissue banking is only permitted if the tissue is being banked for purposes directly related to the study at hand (i.e. the tissue banking must be integral to the study, such that there would be no study if the participant did not contribute the tissue). It is unethical to require that participants agree to allow their tissue to be banked for future use or experimentation that is unspecified or unrelated to the study at hand as a condition for entry into a therapeutic trial, as this could be perceived as a coercive method of obtaining tissue/blood samples through offering a perceived therapeutic opportunity.

Participants may voluntarily donate their tissue for future, unspecified uses provided that the following conditions are made explicit in the main consent form for the study: a) that such donation is optional, and b) that the Investigator discloses whether or not they plan to seek the participants' consent for future projects involving their tissue.

Medical Scans

If medical scans with radiation are required, indicate the level of radiation to which the participant is exposed in a way that a participant can understand (e.g. compared to standard procedures such a chest x-ray). A section under "Risks and Discomforts" should indicate the risks associated with medical scans, as appropriate.

Interview / Questionnaires

If the research study includes interviews or questionnaires, describe the general purpose of the questionnaires (e.g. participant's health status, functional status, quality of life, etc.). Add a note that the participant may refuse to answer questions he/she is not comfortable with.

For interview(s)/questionnaire(s) that may be upsetting to the respondent (i.e. induce embarrassment, humiliation, lowered self-esteem, guilt, conflict, anger, distress or any other negative emotional state), include referrals for counseling and other services, where appropriate.

Health Records and use of data from secondary sources

The consent form should indicate if the participant's health record will be reviewed or excerpts extracted from it. If data is collected from secondary data sources, the consent form must include all of the requirements of TCPS 3.2.

For studies accessing records maintained by the Saskatchewan Ministry of Health, the consent must explicitly make reference to:

- why the information is required from the Ministry of Health
- which services the individual is providing consent for the Ministry to release (e.g., doctor visits, prescription drug information)
- the type of information which would be included on those services (e.g., date of a visit, the diagnosis, type of service provided (e.g., annual physical examination), type of physician (e.g., family doctor or a specialist), etc.)
- the time period over which the services were received (e.g., specify which years or the number of months/years before or after a certain time such as the date the survey is being conducted)
- their health services number and health care records remaining confidential

Optional Sub-Studies

A separate section should be used to describe any studies that are not part of the main study and for which separate consent must be obtained, for example, tissue and blood banking studies; pharmacokinetic studies, analysis of secondary data from linked databases.

Optional sub-studies involving tissue banking and genetic testing are best presented in a separate consent form. Requiring a separate information and consent for genetic testing better assures particular regard for the privacy and confidentiality issues that genetic testing may warrant. Nesting all of the information relevant to genetic testing within a larger protocol and consent form tends to reduce a research participant's particular attention to these matters.

Suggested wording

Even if you choose to take part in this study, the following sub-study is optional. This optional study is for*...{define purpose of sub-study}*. It requires*...{define requirements such as additional blood draws or questionnaires}*. You can take part in the main study and not take part in the optional sub-study. You can indicate your wish on the last page of this form or by signing a separate consent form *[as applicable]*.

WHAT ARE MY RESPONSIBILITIES?

This section is not required for all studies. It is used to list and specify any requirements of the study that the participant must comply with in order to participate. For instance, requests to complete a daily diary, to report any changes in health or to contact their study doctor before taking any medication, natural products or herbal remedies other than the study drug could be listed here.

Suggested wording

As a study participant, you will be expected to:

a. Follow the directions of the Principal Investigator
b. Report all medications being taken or that you plan on taking
c. Report any changes in your health to the Principal Investigator
d. [List other participant responsibilities, such as birth control or pregnancy reporting requirements for both male and female participants and partners, as applicable]

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

This section is required for all studies. It is used to identify benefits to participant, if any. This information should include relevant information about the nature of the potential benefits, stated in an even-handed manner, with both excessive pessimism and undue optimism to be avoided. Alternatively, it should also be mentioned if no direct benefit to participants is anticipated.

If medical treatment is involved, a statement should be added that beneficial effects cannot be guaranteed. Financial compensation and medical tests at no cost to the participant are NOT considered benefits of participation in the study and should not be included in this section.

In research projects where there may be anticipated benefits to society or to a specific group, these potential benefits may be explained in a separate sentence / paragraph so as not to confuse potential benefits to others with potential benefits to the research participant.

In some studies, clarify whether or not the investigators can / will provide the participant with the results from the study, which in some cases may be considered a benefit.

Suggested wording

If you choose to participate in this study, there ... *{may/will or may/will not be direct benefits}* to you}. It is hoped the information gained from this study can be used in the future to benefit other people with a similar condition.

The study may lead to the development of commercial products but there are no plans to share with you any financial profits resulting from the use of your samples or data.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

This section is required for all studies that pose more than minimal risk to a research participant. It is usually best to describe the risks of each procedure in a separate point. Risks should be arranged and described according to their severity and the likelihood/probability of their occurrence. It is helpful to divide risks quantitatively (e.g. rare, less than 1%; common, 1-10%; very common 10-upper %), according to severity and likelihood of occurrence. Excessive use of charts with statistics should be avoided if such use leads to difficulties in the recognition of the main risks associated with the study. References to animal studies are usually omitted unless there is a serious risk likely relevant to humans that is identified. If there is little experience with a new drug or treatment, it is important to state this and that unexpected side-effects may occur. If there is no known risk, a statement may be added to that effect as reassurance to a potential research participant. Where appropriate, it should be indicated how a particular side-effect may be recognized, what precautions will be taken to avoid certain side effects and what will be done should they occur.

Suggested wording

While on the study treatment, you may experience side effects. There may be side effects that are not known at this time. Most side effects go away when you stop taking the study drug. Others may be long-lasting or permanent.

Up to now, there has been *{number}* of people exposed to the study drug.

The following side effects are very common, occurring in *10-[insert upper %]* of people taking the drug: *{list}*

The following side effects are common, occurring in *1-10%* of people taking the drug: *{list}* The following side-effects are rare, occurring *in less than 1*% of people taking the drug: *{list}*

Placebo risk **(if applicable)**

In the case of a placebo-controlled study, the chance of being assigned to the placebo arm of the study should be stated along with the possible consequences of withholding therapy for a particular condition. The right to withdraw from the study should a participant's condition worsen should be clearly stated.

Suggested wording

You have {probability} of being assigned to the group receiving a placebo. A placebo looks identical to the study drug / device but contains no active ingredients. If you or your study doctor feels your condition is getting worse than expected, you may be withdrawn from the study and offered appropriate care.

Reproductive risks **(if applicable)**

There must be special attention paid to a study medication or treatment that may pose a risk to developing fetuses or to babies who are being breastfed. Any birth control requirements (specify type of birth control) or pregnancy reporting requirements should be listed in this section for both male and female participants (and partner).What will happen in the event of a pregnancy (withdrawal from the study and with the participant's permission, follow-up) should be described. In the event of a pregnant partner of a research participant, the request for follow-up should be "with permission". It should be indicated if a separate consent form will be used to request the pregnancy follow-up.

Suggested wording

The medication or treatment used in this study may pose a risk to a developing fetus or a baby who is being breastfed. If you are a sexually active woman capable of becoming pregnant (sexually mature woman who has not undergone a hysterectomy or who has not been post-menopausal for 24 consecutive months), you must use a medically approved effective method of birth control, or you must not have sexual intercourse that could result in pregnancy while on {name of drug or treatment} and for {xxx months} after stopping it. Acceptable methods of birth control are {…list}. Women who are breastfeeding are not eligible to participate in this study.

If you are a man and capable of fathering a child, you must use acceptable methods of birth control every time you have sexual intercourse with a female partner, or you must not have sexual intercourse that could result in pregnancy while on {name of drug or treatment} and for {xxx months} after stopping it.

If you or your partner becomes pregnant while participating in this study, it is important that you notify the study doctor immediately. If you are a female participant, you will be withdrawn from the study. The study doctor will ask your permission (or that of your pregnant partner) to follow the progression and outcome of the pregnancy.

WHAT ARE THE ALTERNATIVES TO THE STUDY TREATMENT?

This section is not required for all studies. When the research includes patients as participants, it is important that the prospective research participant know whether or not there are any alternatives (i.e., other standard treatments) to the treatment that they would receive in the study. If there are alternative therapies, they should be listed, with a note that they will be discussed with the study doctor. If there are no alternative therapies, this should be stated. If the prospective participants are suffering from a terminal illness, and there are no alternative treatments available, the option of supportive care or comfort control measures should be included.

Suggested wording

You do not have to participate in this study to receive treatment for your condition. If you choose not to participate in this study, the following treatment options are available to you: {list them}. Your study doctor will discuss these options with you, including the risks and benefits of each option.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

This section is not required for all studies. During the research study, participants must be given continuing and meaningful opportunities for deciding whether or not to continue participation. Participants should be told that if new information arises during their participation that may affect their willingness to remain in the study, they will be advised of this information. For example, participants would need to be advised if a more effective treatment became available, or if new risks had been identified in relation to their participation in the study.

Suggested wording

During the course of this study, new information that may affect your willingness to continue to participate will be provided to you by the investigator. This includes information about newer, more effective treatments that might become available or any significant change in the risks you are exposed to from your participation in this study.

WHAT HAPPENS IF I DECIDE TO WITHDRAW?

This section is required for all studies. It should explain that the participant can stop participating at any time without penalty. It should also be indicated that the participant does not have to provide any explanation for doing so.

The following information should also be included in this section when applicable:

- If gradual withdrawal is required for safety considerations, explain this and any unique procedure required for timely and safe withdrawal;
- Explain that examinations (physical, blood pressure, blood tests, etc.) may be recommended for safety reasons if the participant decides to withdraw from the study and that these would occur after the participant has been released from the study, with permission of the participant;
- Explain that the investigator will retain any data collected up to the point of the participant's withdrawal from the study, such that the data itself cannot be withdrawn;
- For participants in double-blind studies, explain whether participants will be able to find out what treatment they were receiving.
- In studies where it is not possible to undo the research-related intervention (e.g. somatic cell gene transfer or implantation of medical device) this must be disclosed. However, the participant can withdraw from participation in the research (e.g. the ongoing evaluation) even though the procedures performed cannot be undone.

Suggested wording

Your participation in this research is voluntary. You may withdraw from this study at any time. You do not have to provide a reason. Your future medical care *{or employment or academic status, as applicable}* will not be affected.

If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment will be retained for analysis.

CAN I BE ASKED TO LEAVE THE STUDY?

This section is not required for all studies. It is used to describe under what circumstances the study investigator would take the participant out of the study. For example, the study may be stopped by the sponsor or regulatory agency if knowledge of any unexpected or unexplained serious adverse events that affect participant safety becomes known, the participant needs treatment not allowed in the study, the participant does not follow instructions, became pregnant, or a better treatment has become available.

Suggested wording

The study doctor may decide to discontinue the study at any time, or withdraw you from the study at any time if it is felt to be in your best interests. You may be withdrawn from the study if staying in the study would be harmful, you need treatment not allowed in the study, you fail to follow instructions, you become pregnant, or the study is cancelled by the sponsor for administrative or other reasons.

WHAT HAPPENS IF SOMETHING GOES WRONG?

This section is required for all studies in which there is potential harm to the research participant from participation.

There are three essential statements in this section:

- That in the event of an adverse event, the research participant seeks immediate medical attention.
- That medical attention will be provided at no cost to the research participant.
- That the research participant is not waiving any legal rights to seek compensation for damages by signing the consent form.

Statements concerning availability (or absence) of compensation from the Sponsor for research-related injuries are acceptable, so long as they provide information which may help the potential research participant decide about his/her participation in a research study. Statements off-loading the costs of research-related injuries onto a third party (e.g. the provincial health care plan), are not acceptable without permission of that third party. Neither the REB nor the sponsor can speak on behalf of the Saskatchewan Ministry of Health as to what may (or may not) be covered in the event of a research-related injury.

Suggested wording
Scenario #1

In the case of a medical emergency related to the study, you should seek immediate care and, as soon as possible, notify the study doctor. Inform the medical staff you are participating in a clinical study. Necessary medical treatment will be made available at no cost to you. By signing this document, you do not waive any of your legal rights against the sponsor, investigators or anyone else.

Scenario #2

"In the case of a medical emergency related to the study, you should seek immediate care and, as soon as possible, notify the study doctor. Inform the medical staff you are participating in a clinical study. Necessary medical treatment will be provided. Compensation for other things such as loss of time and income is not provided. By signing this document, you do not waive any of your legal rights against the sponsor, investigators or anyone else."

Scenario #3

In the case of a medical emergency related to the study, you should seek immediate care and, as soon as possible, notify the study doctor. Inform the medical staff you are participating in a clinical study. *{Sponsor}* will pay the medical expenses for any study related injury directly attributable to the trial procedures or the study medications properly administered, as long as you have followed the directions of the doctors in charge of the study. If you are unsure about your ability to follow these instructions, discuss it with the study doctor or a member of the study staff without delay. By signing this document, you do not waive any of your legal rights against the sponsor, investigators or anyone else.

WHAT HAPPENS AFTER COMPLETION OF THE STUDY?

This section is used to provide any information that may be useful to the participant once their participation is concluded. For example, this could include whether or not a participant will be able to continue treatment on the study drug. Availability of the study drug through an extension study or through the Special Access Program may be stated here. If the study drug will not be available after the study ends, some explanations should be provided, with a statement that treatment options will be discussed with the study doctor.

If practical, researchers should also inform participants if/when study results are likely to be available and how to access them. With industry-sponsored research involving study centers worldwide, the results may not be available for several years after the participant his/her participation in the study.

Suggested wording

You {will/may/may not} be able to receive the study treatment after your participation in the study is completed. *{Specify reasons or options, as applicable}* The study doctor will discuss all future treatment options with you at the end of the study.

The results of the study will be available *{time}* from *{Principal Investigator or web site, etc}*.

WHAT WILL THE STUDY COST ME?

This section is required for all studies and is used to stipulate that a research participant will not be charged for study drugs or procedures. This section should stipulate whether or not the participant will incur any personal expenses (e.g., parking, meal, etc.) as a result of participation and whether or not these will be reimbursed. If an honorarium is to be paid (instead of reimbursement for specific expenses), the total dollar amount should be specified, as long as it is not large enough to constitute an "inducement". The honorarium should be presented in the sense

that participants are being reimbursed for their time, travel expenses, and the inconvenience of being a research participant. Participants who withdraw early may not be penalized for doing so and must receive compensation proportionate to their time in the study.

Suggested wording

Scenario #1 – No reimbursement for expenses provided

You will not be charged for the study drug(s) or any research-related procedures. You will not be paid for participating in this study. Reimbursement for study-related expenses (e.g. travel, parking, meals) is not available."

Scenario #2 – Reimbursement for study-related expenses provided

You will not be charged for the study drug(s) or any research-related procedures. You will not be paid for participating in this study. Reasonable expenses for study visits may be reimbursed if they are first discussed and approved by the Study Doctor before the costs are incurred.

Scenario #3 –Fixed Honorarium provided to cover study-related expenses

You will not be charged for the study drug(s) or any research-related procedures. You will not be paid for participating in this study. An honorarium of *{$xxx}* will be provided to cover your time and out-of-pocket expenses such as travel, parking or meals. If you decide to withdraw early from this study, your compensation will be proportional to your time in the study.

WILL MY PARTICIPATION BE KEPT CONFIDENTIAL?

This section is required for all studies. It is used to remind a research participant of his/her privacy rights and to disclose where, how and for how long the information collected will be kept. There are two main concerns: **anonymity** (how will the investigator prevent identification of participants in a study) and **confidentialit**y (what steps are taken by the researchers to safeguard access to the information collected). This section should also be used to inform the research participant if their family physician should/will be informed of participation in the study.

If and how the information will be de-identified should be clearly stated (e.g. use of unique study code and/or scrambled initials). For all statements regarding confidentiality of research records, it should be kept in mind that there is no legal privilege between investigator and participant as there is between physician and patient or counselor and client. Thus, a guarantee of complete confidentiality, or "strictest confidentiality," should not be given or implied. In rare instances it will not be possible to ensure confidentiality because of mandatory reporting of reported child abuse, communicable diseases, etc. When this is the case, the participants should be made aware of this limitation in the consent form.

Suggested wording
Scenario #1

In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected. Your name will not be attached to any information, nor mentioned in any study report, nor be made available to anyone except the research team. It is the intention of the research team to publish results of this research in scientific journals and to present the findings at related conferences and workshops, but your identity will not be revealed.

Scenario #2

In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected.

Your study records will be identified by ***{indicate de-identification protocol}***. They will be kept for ***{XX years}*** in a secure area such as a locked file cabinet and office ***{at research center}***.Tissue samples and results of the study without your name or other information that could identify you will be sent to ***{sponsor and …}*** and combined with information from other participants for analysis.

No information that discloses your identity will be released or published without your specific consent. Some authorities have a duty to check your study and medical records to make sure all the information is correct. Your study and medical records may be inspected in the presence of the investigator or his/her qualified designate by representatives of (insert here, if relevant to study- the study sponsor, Health Canada, the U.S. Food and Drug Administration and the ***{institutional}*** Research Ethics Board).

If you decide to withdraw from this study, your study and medical records will be made available to these agencies. However, they will only look at your records up to the date of your withdrawal, except where the reporting of side effects associated with the study medication is required. Rarely, your study documents may be obtained by courts of law. You may ask the study doctor to see and copy your personal health information related to the study. You may also ask the study doctor to correct any study related information about you that is wrong. In the case of a blinded study, you may have to wait until the end of the study to see your study records to protect the integrity of the study.

The results of this study may be presented in a scientific meeting or published, but your identity will not be disclosed.

For your own safety, it is strongly recommended that your family physician be informed of your participation in this study. With your permission, he/she will be informed and may be consulted regarding your health and treatment.

For studies that in the researcher's judgment pose significant health risks to the participant, the requirement to inform the family physician may be mandatory, but the participant must be informed of this requirement.

Suggested wording:
For your safety, your family physician will be informed of your participation in this study and may be consulted regarding your health and treatment.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

This section is required for all studies. It is used to provide contact information for the Principal Investigator for questions about the study and to the Research Ethics Board for questions concerning the participant's rights and experiences as a research participant.

Suggested wording

If you have any questions or desire further information about this study before or during participation, you can contact *{Principal Investigator or his/her representative}* at *{telephone number}*.

If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Chair of the University of Saskatchewan Research Ethics Board, at 306-*966-2975(out of town calls 1-888-966-2975)*. The Research Ethics Board is a group of individuals (scientists, physicians, ethicists, lawyers and members of the community) that provide an independent review of human research studies. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Research Ethics Board.

PARTICIPANT CONSENT TO PARTICIPATE

This section is required for all studies. The participant is signing the form to indicate that he/she has either read (or otherwise been informed), and understands the information concerning the study. The first person pronoun ("I") is used for this section. Contractual-sounding language should be avoided and it should be clear that the participant does not give up any legal rights by signing it.

In cases of minors or individuals with cognitive handicaps unable to provide consent, the TCPS places certain conditions on when these individuals can be invited to participate in research (see articles 2.5, 2.6, 2.7 and 5.3). If these conditions are met, it should be determined whether a parent, guardian, or other representative has the legal authority to give consent to the proposed research, and if so, that individual's consent must be obtained. An assent form in appropriate language for minors or adults without capacity should also be used, when applicable. If not, the form should indicate that assent from the participant has been obtained even if the parent/proxy has consented. A means of recording that assent was obtained (signature line with yes/no checkboxes) should be included in the consent form, if an assent is not used. Individuals, who verbally or behaviourally indicate that they do not wish to participate, must be allowed to withdraw even when proxy consent has been given. If a participant becomes able to consent on his or her own behalf during the course of the study, this consent must be obtained in order for the participant's participation to continue.

There is no clear basis in Saskatchewan law for a "legally authorized representative" to make decisions for a non-competent individual <u>for research purposes.</u> It is the researcher's responsibility to ensure that the person providing consent has the authority to do so. It is suggested that the "authorized representative" be defined, for example:

"An authorized representative in this study is the person who has the authority to make a decision about participation in the study on behalf of a participant who does not have the capacity to decide, as the participant's parent or guardian or as someone who was entrusted by the participant to make such decision when the participant was competent. The authorized representative should decisions according to the participant's wishes and best interests."

If the consent form is being translated verbally for the research participant, then the translator must also sign the consent form indicating that the translation was to the best of his/her ability.

The signature of a witness is optional. It is not required by law but is recommended by the International Conference on Harmonization (ICH) / WHO Good Clinical Practice standards (ICH-GCP).

A copy of the signed and dated consent form must be given to the participant.

Suggested wording

CONSENT TO PARTICIPATE

- o I have read (or someone has read to me) the information in this consent form.
- o I understand the purpose and procedures and the possible risks and benefits of the study. o I have been informed of the other treatments available for my condition.
- o I was given sufficient time to think about it.
- o I had the opportunity to ask questions and have received satisfactory answers.
- o I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future medical care.
- o I agree to follow the study doctor's instructions and will tell the study doctor at once if I feel I have had any unexpected or unusual symptoms.
- o I have been informed there is no guarantee that this study will provide any benefits to me.
- o I give permission for the use and disclosure of my de-identified personal health information collected for the research purposes described in this form.
- o I understand that by signing this document I do not waive any of my legal rights. o I will be given a signed and dated copy of this consent form.

- o *(If applicable)* I agree to participate in the optional sub-study on *{define}* ❑ Yes ❑ No
- o My family physician can [or will] be informed about my participation in this study, and, if required, consulted regarding my health and treatment.
  - ❑ Yes, you may contact my primary care physician
  - ❑ No, please do not contact my primary care physician
  - ❑ I do not have a primary care physician.
- o *(If applicable)* I grant the Saskatchewan Ministry of Health permission to disclose my health care information to the study researchers ❑ Yes ❑ No

I agree to participate in this study:

Printed name of participant: Signature Date

Printed name of person obtaining consent: Signature Date

Informed Consent Form

A Randomized, Double-Blind, Placebo Controlled Phase II Study of L-Alanyl-L-Glutamine For the Reduction of Peritoneal Adhesions in Adult Females Undergoing a Myomectomy

Research Participation Information Sheet

Research Participation Information Sheet

Principal Investigator: Dr. Donna R. Chizen, MD

Tel: (306) 966-8623

Fax: (306) 966-2981

Email: donna.chizen@usask.ca

Research Supervisor: Dr. Roger A. Pierson

Tel: (306) 966-4458

Fax: (306) 866-8796

Email: pierson@erato.usask.ca

Study Coordinator: Dominique Singh, BSN, RN

Tel: (306) 292-7756

Fax: (306) 966-8796

Email: dominique@adetherapeutics.com

24-hour Emergency Contact: Dominique Singh

Tel: (306) 292-7756

Funder: AdeTherapeutics, Inc

You are invited to participate in this study because you have uterine fibroids and will be undergoing a surgery to remove the fibroids. Fibroids are also called uterine myomas and the surgery to remove a fibroid is called a myomectomy. You are considering volunteering in a research study that is conducted by the Women's Health Imaging Research Laboratory in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of Saskatchewan, Saskatoon, Canada. Before you give your consent to be a research participant, please read this information sheet and ask as many questions as necessary to be sure that you understand what your participation will involve. Your participation is entirely voluntary, so it is up to you to decide whether or not to take part in this study. If you do decide to take part in this study, you are free to withdraw at anytime without giving any reason for your decision nor will you lose the benefit of any medical health care to which you are entitled or are presently receiving.

This research will be conducted at the Women's Health Imaging Research Laboratory in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of Saskatchewan. The study site will be through the Department of Obstetrics and Gynecology at the Royal University Hospital and Saskatoon City Hospital in Saskatoon, Saskatchewan.

The Funder of this study, AdeTherapeutics, will reimburse your doctor and the clinic hospital for the costs of undertaking this study. However, neither the institution nor any of the investigators or staff will receive any direct financial benefit from conducting this study. The study may lead to the development of commercial products. There are no

plans to share with you any financial profits resulting from the use of your samples or data.

Purpose of the study:

Adhesions are abnormal deposits of fibrous scar tissue that can form within the abdomen. Inflammation and adhesions form as the body attempts to repair itself after inflammation, infection or injury. Abdominal adhesions around the reproductive organs are common causes of pelvic pain and infertility. Up to 97% of gynecological surgeries can result in adhesion formation.

Currently, there is no standard of care to prevent post-operative adhesions. Various methods of adhesion prevention and treatment have been tried but they have had limited success. The purpose of the present study is to characterize the adhesion reduction effect of L-Alanyl-L-Glutamine after pelvic surgery. Glutamine is an essential amino acid that the body is unable to make on its own in sufficient quantity under circumstances such as surgery. The study drug, which is compromised of L-Alanyl-L-Glutamine is safe and well absorbed in the body. Many people currently take it orally or by injection as a nutritional supplement. However, L-Alanyl-L-Glutamine has not yet been examined in humans to prevent adhesions. We have performed preliminary studies in animals that demonstrate that it is very effective in reducing adhesion formation following surgery. On the basis of these trials, we expect that the compound will significantly reduce the number and severity of adhesions following human surgical procedures.

Procedures:

Approximately 40 women who have been diagnosed with uterine fibroids and meet all the necessary requirements for entry into the study will be asked to participate. If you are selected and choose to participate, your total participation time will be approximately eight (8) weeks. Once you have signed the consent form you will be randomly assigned to either the treatment group or the placebo group. Random assignment is an experimental technique used to divide research participants into treatment and non-treatment groups without creating bias. A placebo is a substance that looks like and is given exactly like the drug, but contains no active medical ingredients. The study is double-blinded which means that the study coordinator, principal investigator, surgeon and any other hospital staff involved in your care do not know what group you are assigned to. In the event of a medical emergency, the blind can be broken to ensure proper medical care and safety.

The surgery procedure that you will undergo is a myomectomy, which is a standard surgical procedure for the removal of uterine fibroids. The location of the fibroids will be determined and removed, as per normal procedures. For study purposes, before the surgery is finished, your surgeon will apply either the treatment drug (L-Alanyl-L-Glutamine) or the placebo to the area. During the surgery, digital video and photographs will be taken of the affected area for the study and stored in our study files. You will be admitted to a surgical ward for standard post-operative monitoring and care. In

conjunction with the study, you will receive any and all standard follow-up care that your surgeon requires. (See Saskatoon Health Region's Surgical Check-List attached)

Upon discharge from the hospital, you will be given a diary card with a number a questions. You will be required to answer these questions at the end of each week for eight (8) weeks. The study coordinator will conduct telephone check-up interviews 1, 4 and 7 weeks after your surgery. These interviews will consist of a few questions related to your diary card and any pain or symptoms you may be feeling post-operatively. For study purposes, on week 6-8 you will be required to report back to the hospital for a follow-up second-look laparoscopic procedure. During the follow-up surgery, digital video and photographs will be taken of the your reproductive organs. Any adhesions that are present will be assessed, photographed and removed. These follow-up conversations, tests and surgery allow the research team to ensure that you are receiving the highest quality of care.

Schedule of Assessments

Assessment	***Pre-operative Assessment***	***Myomectomy***	***Post-Operative Care***	***6-8 Week Follow-up***
Informed Consent	*X*			
Inclusion/Exclusion Criteria	*X*			
Physical Exam	*X*	*X*	*X*	
Vital Signs	*X*	*X*	*X*	
Laboratory Assessments	*X*	*X*	*X*	
Pre-op Parameters	*X*	*X*		
Treatment		*X*		

Administration				
Surgery		*X*		*X*
Adhesion Assessment		*X*		*X*
Adverse Events		*X*	*X*	*X*

You will be asked to sign 2 copies of the Research Participant Information Sheet and attached Consent Form after having thoroughly read and reflected on them before initiating any study procedures. A witness may be present when you sign the Consent Form. One copy of the information sheet and consent form will be retained in our study files and one copy will be given to you for your records.

Research Related Injury Statement:

In the event that you become ill or injured as a result of participating in this study, necessary medical treatment will be made available at no additional cost to you. By signing this document you do not waive any of your legal rights. In case of a medical emergency, you should seek immediate care, and as soon as possible, notify the study doctor.

Foreseeable Risks and Discomforts:

There are no expected side effects associated with L-Alanyl-L-Glutamine.

The use of the treatment drug or the placebo should not pose any risks or discomforts.

The risks of the myomectomy surgery may include bleeding, trauma and infection, will be discussed with you by your surgeon prior to your surgery. Your surgeon will discuss the method for removing fibroids (myomectomy) by either laparoscopy or by laparotomy that is the preferred method to provide you with the best care. No additional surgical risks are anticipated as a result of participating in the study.

The 6-8 week follow-up laparoscopic surgery is a necessity of the study. It is important to see if any scar tissue has formed after receiving the study drug or placebo. The risks of a second laparoscopy are similar and may include bleeding, trauma and infection, and will again be discussed with you by your surgeon.

Benefits of the Study:

You may benefit from the follow-up surgery because scar tissue around the uterus, fallopian tubes, bowel and belly wall can be removed if present. During the study, we may see that women who received the study drug during surgery have less scar tissue than women who received the placebo.

It is hoped the information gained from this study can be used in the future to benefit other people with a similar condition. If you choose to participate in this study, there may or may not be any direct benefit to you.

Compensation:

You will not be charged for the study drug(s) or any research-related procedures. You will not be paid for participating in this study. An honorarium of $250.00 will be provided to cover your time and out-of-pocket expenses such as travel, parking or meals. If you decide to withdraw early from this study, your compensation will be proportional to your time in the study. Because this honorarium is over $50.00 your Social Insurance Number (SIN) will be forwarded to financial services at the University of Saskatchewan for taxation audit purposes.

Confidentiality:

In Saskatchewan, the Health Information Protection Act (HIPA) protects the privacy of your personal health information. Your privacy will be respected.

Your study records will be identified by a number assigned to you at the beginning of the study. They will be kept for 20 years in a secure area such as a locked file cabinet. Results of the study without your name or other information that could identify you will be combined with information from other participants for analysis.

No information that discloses your identity will be released or published without your specific consent. Some authorities have a duty to check your study and medical records to make sure all the information is correct. Your study and medical records may be inspected in the presence of the investigator or his/her qualified designate by representatives of Health Canada or the University of Saskatchewan Research Ethics Board.

If you decide to withdraw from this study, your study and medical records will be made available to these agencies. However, they will only look at your records up to the date of your withdrawal, except where the reporting of side effects associated with the study medication is required. Rarely, your study documents may be obtained by courts of law. You may ask the study doctor to see and copy your personal health information related to the study. You may also ask the study doctor to correct any study related information about you that is wrong. In the case of a blinded study, you may have to wait until the end of the study to see your study records to protect the integrity of the study.

The results of this study may be presented in a scientific meeting or published, but your identity will not be disclosed.

For your own safety, it is strongly recommended that your family physician be informed of your participation in this study. With your permission, he/she will be informed and may be consulted regarding your health and treatment.

Alternatives to Participation in this Study:

You do not have to participate in this study to receive treatment for your condition. If you choose not to participate in this study, you will still receive standard of care treatment for your uterine fibroids. Your study doctor will discuss the options with you, including the risks and benefits of each option.

Voluntary Participation/Withdraw from the Study:

Your participation in this study is purely voluntary. You may decide not to participate or may withdraw at any time. Your refusal to participate in, or your withdrawal from, the study will not affect your medical care in any way. If you wish to withdraw from the study, please notify any member of the Research Team as soon as possible and the appropriate arrangements will be made.

Your participation in this study may be ended at any time, without your consent. Reasons may include, but are not limited to, your failure to follow study instructions, the appearance of side effects, or study cancellation due to administrative reasons.

The blinded nature of this study does not allow for information about the study to be revealed until the entire study is completed. Once the study has been completed, it is

possible for you to receive the results of the study. If you are interested in understanding and learning about the results, please ask the study coordinator for this information.

Questions Regarding Participation:

If you have any questions regarding your participation in this study, please feel free to call:

Principal Investigator: Dr. Donna R. Chizen, MD

Tel: (306) 966-8623

Fax: (306) 966-2981

Study Coordinator: Dominique Singh, BSN, RN

Tel: (306) 292-7756

Fax: (306) 966-8796

If you have any questions about your rights as a participant or concerns about the study, you should contact the Chair of the Biomedical Research Ethics Board, c/o the Ethics Office, University of Saskatchewan at 966-4053.

Consent Form

I have read and understand the attached Research Participant Information Package, and I freely and voluntarily agree to take part in the study entitled ***A Randomized, Double-Blind, Placebo Controlled Phase II Study of L-Alanyl-L-Glutamine For the Reduction of Peritoneal Adhesions in Adult Females Undergoing a Myomectomy.***

I have been given a copy of the Research Participation Information Package and will be given a copy of the signed and dated Consent Form. I have received an explanation of the purpose and duration of the trial, and I am aware of the potential benefits and side effects associated with the procedures involved in this study.

I was given sufficient time and opportunity to ask questions, to reflect on my understanding of and participation in the study. My questions have been answered to my satisfaction.

I agree to cooperate fully with the study personnel and will tell him/her of any medicine, drug or alternative therapy (herbal remedy) of whatever nature I have taken in the recent past, or am taking now, whether prescribed or not.

I understand that I am free to withdraw from the study at anytime, for any reason, and this will not affect my future medical treatment.

Please check the appropriate box to indicate your decision:

_____ Yes, I agree that the research study staff may inform my family doctor of my participation in this study.

_____ No, I do not want you to inform my family doctor of my participation in this study.

_____ _____

Signature of Participant Date

Printed name of above: _____

I confirm that I have explained the purpose and procedures of this study, as well as any potential risks and benefits, to the participant whose name and signature appears above.

_____ _____

Signature Date

Printed name of above: _____

Study Role: _____ Initials: _____

AdeTherapeutics Inc

L-Alanyl-L-Glutamine

INVESTIGATOR'S BROCHURE

Edition Number: 002

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1.0 Confidentiality Statement

Sponsor:

AdeTherapeutics Inc.

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Canada S7N 4N1

Investigational product:

L-Alanyl-L-Glutamine

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002

Confidentiality Statement

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document is strictly prohibited without the express written consent of the designated lead or principal investigator.

_____

Signature

Dr. Donna Chizen

Principal Investigator

2.0 Summary

The active ingredient L-Alanyl-L-Glutamine that will be investigated in this study is a conditionally-essential amino acid that is naturally occurring in the body. The formulation of alanyl-glutamine that will be used in the study has a pH of 6.0 ± 0.5 and has a concentration of 400mg/mL alanyl-glutamine. This investigational product will be provided in 20mL type I clear glass vials and has a recommended storage condition of (2-8°C). An intra-abdominal bolus injection route will be used at a dose of 1g/Kg of body weight to investigate the safety and tolerability of alanyl-glutamine in the prevention or reduction of adhesions following abdominal surgery in humans.

L-glutamine has an established history of positive safety outcomes in both animal and human trials. In animals, glutamine clearance occurs primarily through the liver and kidneys. In humans, most often renal clearance has higher rates than splanchnic organs and muscle tissue. Animal and human safety studies have also shown relatively short half-lives of L-glutamine. The literature suggests that high doses of glutamine (up to 1.5 g/Kg body weight in animals; 0.57 g/Kg body weight in humans) can be given with little to no pharmacological or physiological change in either animals or humans.

To date, L-glutamine has been given to humans via oral, intravenous, enteral and parenteral routes. This study is a first in man for an intra-abdominal route of administration. The existing pharmacological, pharmacokinetic and clinical evidence available in the scientific literature provides confidence for the investigation of a single bolus dose of 1g/Kg body weight L-Alanyl-L-Glutamine to surgical patients undergoing myomectomy.

3.0 Introduction

Glutamine is considered a non-essential amino acid that is found readily within the human body. It plays an important role in muscle metabolism and is the preferred energy source for cells of the intestinal mucosa and the immune system, particularly macrophages and lymphocytes (Windmueller & Spaeth, 1980; Calder, 1994). Most recently, in vitro studies of alanyl-glutamine's effect of mesothelial cells of the peritoneum have suggested a cytoprotective role for A-G on peritoneal tissues specifically (Kratochwill, 2012). Glutamine can become "conditionally essential" during inflammatory conditions such as infection and injury (Newsholme, 2001). Glutamine, as a free amino acid, is unstable on its own. It has limited solubility in water and quantitative decomposition of aqueous glutamine to the cyclic product associated with ammonia liberation (Furst, 2001). L-Alanyl-L-Glutamine (A-G) is a dipeptide of glutamine that is stable during heat sterilization and is highly soluble.

Alanyl-Glutamine has been used most commonly as a nutritional supplement (intravenous, enteral and parenteral). When infused enterally, it increases intestinal villous height, stimulates gut mucosal cellular proliferation, and maintains mucosal integrity (Miller, 1999). It can also prevent intestinal hyper-permeability and bacterial translocation, which may be involved in sepsis and the development of multiple organ failure.

The idea that alanyl-glutamine might have potential in the prevention or reduction of adhesions following abdominal surgery was first investigated by Dr. Adebola Obayan, at the University of Saskatchewan, Canada. In pioneering studies conducted by Obayan, a sham operation in which a cecal perforation with purse string repair to prevent peritonitis was performed on 80 Wistar rats. A-G, saline, or vehicle was administered directly into the

abdominal cavity before the abdomen was sutured. At specific time points following the surgery (3,7,10,14,21,42 and 90 days) the rats were evaluated for adhesions. Obayan found that the rats treated with A-G demonstrated a significant decrease in adhesions compared to the group that did not receive any treatment.

The rationale for clinical development of alanyl-glutamine for the prevention or reduction of adhesions following abdominal surgery in humans derives from the positive results of Obayan's initial work in an animal model. This rationale has since gained indirect corroboration from the work of Aurefct (2014), Kratochwill (2012) and others, studying the cytoprotective effects of A-G in the recovery of mesothelial cells of the peritoneum from the insult of peritoneal dialysis fluid. The first trial will be conducted on patients diagnosed with uterine fibroids undergoing myomectomy. Alanyl-glutamine will be administered into the peritoneal cavity before the patient's incision is closed. The patient will be reassessed 6-8 weeks post-operatively during a second look laparoscopic procedure. Incidence and severity of any adhesions will be assessed, scored and compared between patients receiving the treatment and patients receiving the placebo (WFI).

4.0 Physical, Chemical and Pharmaceutical Properties and Formulation

4.1 ***Chemical and Physical Properties***

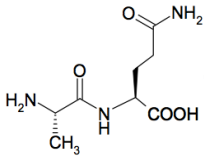
4.1.1 **Active ingredient**

L-Alanyl-L-Glutamine

4.1.2 **Molecular formula**

$C_8H_{15}N_3O_4$

4.1.3 **Structural formula**



4.1.4 **Relative molecular mass**

217.23

4.1.5 **Chirality**

L-form

4.1.6 **Physical state**

White crystals or crystalline powder

4.1.7 **Solubility**

568g/L in H_2O (20^oC)

4.1.8 **pH**

6.0 ± 0.5

4.1.9 **Osmolality**

190 mOsm/kg (dilute sample to 40mg/ml using USP water)

4.2 *Pharmaceutical and Formulation Stability*

4.2.1 **Strength/Potency**

400 mg/mL

4.2.2 **Dosage Form**

Injection

4.2.3 **Package Size**

20 mL Type I clear glass vial

4.2.4 **Storage Conditions**
Refrigerate (2-8°C)

4.2.5 **Sterility**
No growth observed – Meets requirements

4.2.6 **Volume in Container**
20.9 mL

5.0 Non-Clinical Trials

5.1 ***University of Saskatchewan Trial***

As described above, preliminary non-GLP efficacy studies of L-Alanyl-L-Glutamine in rats were conducted by A. Obayan at the University of Saskatchewan. The results demonstrated that L-Alanyl-L-Glutamine reduced the incidence and severity of adhesions in animals treated intra-abdominally with the drug at the time of surgery, as compared to animals treated with saline only or animals that did not receive either treatment or carrier.

In one definitive study, male Wistar rats (n=70) were divided into five groups corresponding to three Treatment and two Control groups. The Treatment groups underwent open surgery that involved a midline sub-umbilical incision and a modified cecal puncture with purse string repair. L-Alanyl-L-Glutmaine (0.3g/kg-1.5g/kg); saline (5 ml); or L-glutamine (1.5g/kg) was instilled into the abdominal cavity from a syringe. Control Group 1 was comprised of animals on which no surgery was done (virgin abdomen). Control Group 2 was comprised of animals that received surgery but did not receive drug or placebo at the time of closure.

At ninety days following surgery, the animals in all five groups were reopened and assessed visually for incidence and severity of adhesions. A Zuhlke score (Zuhlke et al., 1990) was applied to estimate severity of the adhesion (Grade 0– no adhesion, Grade 1– flimsy adhesion, Grade 2– mild adhesion, Grade 3– moderate adhesion, Grade 4– severe adhesion). The process of acute inflammation was assessed based on the immunohistochemical detection of MCP1 (macrophage chemotactic protein) and the number of macrophages. The average number of milky spots per high-powered field was determined as well. Milky spots (composed of macrophages, B-lymphocytes and leucocytes) are tissue structures found in the omentum and, an increase in their numbers and size are indicative of adhesion formation. Fibrosis and collagen formation were also assessed.

The results of the visual scoring indicated that adhesions in L-Alanyl-L-Glutamine treated rats were absent or reduced by about 80% ($p \leq 0.05$) following abdominal surgery compared to saline or untreated controls. Histological examination revealed that fibrosis and collagen formation assessed ten days after surgery were significantly reduced in animals treated with L-Alanyl-L-Glutamine or L-Glutamine. The level of MCP1 expression and macrophage number tended to be reduced in rats treated with A-G or L-Glutamine compared to the untreated animals or rats treated with the saline solution, although this was not a statistically significant observation. No complications, including deaths, were observed in the group of rats treated with L-Alanyl-L-Glutmaine compared to the surgical control groups (i.e., no treatment, saline only treatment). Furthermore, within the same surgical control groups, milky spots count were 49 and

35 per 7 high power field, respectively, whereas the no surgery and treated group had 1 milky spot per 7 high power field.

These data support the hypothesis that L-Alanyl-L-Glutamine, administered intra-abdominally during surgery, just prior to closure of the surgical wound, is effective at reducing or preventing abdominal adhesions that typically arise following surgery.

5.2 *Non Clinical Pharmacology*

Non Clinical Pharmacology studies of L-Alanyl-L-Glutamine are not necessary to support the proposed Phase I Study, as per NOTE FOR GUIDANCE ON SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS (CPMP/ICH/539/00), Section 2.9, Conditions Under Which Studies Are Not Necessary.

The Test Substance in the Phase I Study described in this brochure, will be administered locally to the peritoneum and has been well characterized in humans (see Section 6, EFFECTS IN HUMANS, below). The Test Substance will be dosed as described in this brochure, directly into the peritoneum, as a single bolus of 1g/Kg body weight. This dose is within the approved range of parenteral doses of commercial L-Alanyl-L-Glutamine products, such as Fresenius Kabi's Dipeptiven®. Dipeptiven® is a Total Parenteral Nutrition product given to critical care patients in hospital settings that is infused for up to five days at 0.3g-0.5 g/Kg /day. It is formulated in an aqueous presentation, similar to that of the test product to be used in this study.

5.3 *Pharmacokinetics and Product Metabolism in Animals*

Adibi et al. (1986) conducted a study in rats to investigate the influence of positioning of different amino acids in the N-terminus on the peptide metabolism. Glycyl-glutamine and alanyl-glutamine (0.5 micro-mol/g body weight) were injected into a tail vein. Plasma concentration of

glycyl-glutamine, alanyl-glutamine and glutamine was measured after blood was taken at the regular intervals before and after (0, 2, 4, 6, and 10 min) each injection. Half-life for alanyl-glutamine was shorter (0.7 ± 0.1 min) then for glycyl-glutamine (3.1 ± 0.8 min). The rate of renal excretion was measured 15 minutes after injection of each dipeptide. The rates of renal excretion for alanyl-glutamine and glycyl-glutamine were 1.9 ± 0.2 and 3.1 ± 0.3 micro-mol/15min respectively. Urinary excretion of glutamine was 2 times higher when alanyl-glutamine was injected.

Abumrad et al (1989) investigated the clearance of glycyl-glutamine and alanyl-glutamine by liver, kidney, gut and muscle tissue in 18 hour fasted dogs. Dipeptides were injected at the rate 12 micro-mol/min/kg. Plasma concentration was higher for glycyl-glutamine 1,113 ± 57 micro-mol vs. 308 ± 17 micro-mol for alanyl-glutamine. Metabolic clearance excretion rate was higher for alanyl-glutamine comprising 40.2 ± 2.6 ml/min/kg vs. 11.0 ± 0.5 ml/min/kg for glycyl-glutamine. The liver and kidney were involved in the metabolic clearance of alanyl-glutamine at similar rates, which were approximately two times higher then those for gut and muscle.

Metabolism of the highly soluble solution of radioactively labeled alanyl-glutamine was administered by intravenous to rats (Stehle, 1989). Three hours after bolus administration the amount of recovered alanyl-glutamine was 56% in CO_2, 13% in muscle, 3.1% in liver, 1.9% in plasma and 0.6% in kidney of the injected dose. Stehle found that alanyl-glutamine was hydrolyzed immediately and is, therefore, a suitable source of glutamine.

5.4 *Toxicology in Animals*

Tsubuku et al. (2004) conducted a safety study on 75 Sprague-Dawley rats. Glutamine, as dietary supplement, was administered over a period of 13 days. Glutamine was supplemented at 1.25%, 2.5% and 5% of the standard diet. The control group received the standard diet only. The rats studied displayed no changes in diet consumption, ophthalmologic findings, gross pathology and histopathology. During measurements of urine parameters, alteration of total protein, urine pH and positive incidence of ketone bodies were detected in the groups receiving 2.5% and 5% of glutamine. Several haematology parameters such as platelet count, hemoglobin, and lactate dehydrogenase increased in the group of rats receiving 5% of glutamine. These changes remained in the physiological range.

5.4.1 **Cytotoxicology**

Olney et al (1971) investigated cytotoxic effects of different amino acids on the brain and retina of infant mice. Ten-day-old Webster Swiss albino mice were given 24 different compounds in the form of a single subcutaneous dose. Integrity of cellular structures of the brain and retina were assessed by light and electron microscopy. L-glutamine was shown to have no cytopathic effect at the dose of 12 mmol/kg (1.75 g/kg) and weakly toxic at the dose of 24 mmol/kg (3.5 g/kg) that resulted in the necrosis of a small number of neurons. This group of rats also showed no cytotoxicity in the explants of the peritoneum.

6.0 Effects in Humans

6.1 *Pharmacokinetics and Product Metabolism in Humans*

Lochs et al (1989) investigated organ clearance of glycyl-glutamine and alanyl-glutamine (100 micro-mol/h/kg) constantly infused in human subjects. Similar to the animal data (Abidi,

1986; Abumrad, 1989) plasma concentration for alanyl-glutamine was lower (70 ± 24 micro-mol) than that for glycyl-glutamine (295 ± 22 micro-mol), indicating that alanyl-glutamine is hydrolyzed at a faster rate than glycyl-glutamine one. Metabolic clearance for alanyl-glutamine was higher than for glycyl-glutamine (16.6 ± 1.9 ml/min/kg vs. 6.2 ± 0.5 ml/min/kg) as well. There was no excretion of either dipeptides present in the urine, however, renal release of glycine, alanine and glutamine into the systemic circulation was observed during infusion of each dipeptide. The kidneys had a crucial role in the clearance of glutamine dipeptides from plasma in humans, while the liver and muscle tissue demonstrated a much lower rate of clearance. No adverse reactions were reported in the study.

In a subsequent study by Lochs et al. (1990) organ metabolism of alanyl-glutamine dipeptide infused through intravenous (100 micro-mol/h/kg) was compared to the metabolism of alanine and glutamine introduced in separated amino acid form. Infusion of alanyl-glutamine dipeptide and amino acids lead to increased plasma concentration of glutamine (620 ± 66 vs. 764 ± 65 micro-mol/L before and during the dipeptide infusion and 688 ± 35 vs. 889 ± 46 micro-mol/L before and during the amino acid infusion). Alanine concentrations in plasma were elevated in a similar manner (260 ± 31 vs. 330 ± 38 micro-mol/L before and during the dipeptide infusion and 214 ± 12 vs. 316 ± 9 micro-mol/L before and during the amino acid infusion).

The splanchnic balance of glutamine became positive during infusion of alanyl-glutamine and corresponding amino acids. Muscle glutamine balance was not altered during the infusion of both forms of glutamine. Renal glutamine balance was changed from positive to neutral during the infusion of alanyl-glutamine and remained unchanged during the infusion of corresponding amino acids. Alanine balance in splanchnic organs became significantly more positive and changed from negative to neutral in muscle tissue during both forms of glutamine infusions.

Renal balance of alanine was changed from neutral to negative during the dipeptide infusion and remained unchanged during infusions of corresponding amino acids. Alanyl-glutamine was cleared by kidney at the rate of 51 ± 3 micro-mol/min, which was significantly higher then the splanchnic organ rate, (19 ± 3 micro-mol/min) and muscle tissue rate (21 ± 8 micro-mol/min).

Albers et al. (1988) investigated the pharmacokinetics of alanyl-glutamine in 10 healthy volunteers. Each volunteer received a peptide bolus of 30 mg/kg. Within a 30 min period, blood was taken 18 times to measure the elimination half-life, distribution volume and plasma clearance. Alanyl-glutamine was not detectable 30 minutes after the bolus injection. The estimated elimination half-life for alanyl-glutamine was 3.8 min. The estimated distribution volume was 10.52 Liters. Both estimates showed minimal variations between individuals.

In other series of experiments, Albers et al. (1989) studied constant intravenous infusion of alanyl-glutamine. Alanyl-glutamine was infused in 6 healthy volunteers at the rate of 96 mg amino acids/kg/h over a 4-hour period. The infusion of alanyl-glutamine resulted in increased plasma concentration in both alanine (255.1 ± 100.1 micro-moles above basal level) and glutamine (232.8 ± 38.3 micro-moles above basal level). After the start of the infusion, these results remained in a steady state (60 and 240 micro-moles above basal level). This study suggests that alanyl-glutamine can be safely used as an efficient source of glutamine.

Ziegler (1990) conducted a pharmacokinetic study in four healthy volunteers after a bolus intravenous injection of glutamine. The parameters that were measured and results obtained (shown in parentheses) were as follows; volume of distribution (14.7±2.1 L), elimination rate constant (00.110 ± 0.002 min^{-1}), elimination half-life (12 ± 2 min for initial slop and 67 ± 11 min for terminal slope) and clearance (2.3 ± 0.5 mg/kg/min). Splanchnic uptake of oral glutamine was 84% at the dose of 0.3 g/kg and 57% at 0.1 g/kg. The rapid elimination of the dipeptide

demonstrated in these studies suggests that substantial amounts of alanyl-glutamine can be used with no pharmacological or physiological effects (Furst, 1989).

6.2 *Safety and Efficacy in Humans*

Jiang (1999) conducted a double-blind study in 120 post-operative patients. Blood panels were compared between the treatment group, receiving parenteral alanyl-glutamine and the control group, receiving standard TPN. There were no significant differences found.

Morlion et al., (1998) studied the safety of alanyl-glutamine as part of a TPN infusion. Twenty-eight post-operative subjects undergoing abdominal surgery were used. Each subject received 0.3 g/kg of alanyl-glutamine over 5 days post-operatively. There were no side effects or patient complaints reported. Patients who received the alanyl-glutamine TPN infusion had improved nitrogen balance, improved lymphocyte recovery on day 6 and improved generation of cysteinyl-leukotrienes from polymorphonuclear granulocytes.

Lowe et al (1999), studied the effects of a glutamine supplemented TPN infusions in 7 healthy volunteers. The study was conducted over three 5-day periods with increasing glutamine doses (0, 0.285 and 0.570 g/kg). All diets were well tolerated with no adverse effects. Plasma glutamine concentrations increased significantly but plateaued at concentrations around 25% above control values. Ammonia and glutamate, potentially toxic metabolites of glutamine, had no significant changes following glutamine enrichment. This study was able to conclude that glutamine-enriched TPN is well tolerated with no associated signs of toxicity in normal humans.

Dipeptiven® (L-Alanyl-L-Glutamine) by Fresenius Kabi is a commercially approved product that is indicated for Total Parental Nutrition infusion for critically ill patients. Numerous studies have been conducted to evaluate the efficacy of Dipeptiven® in different clinical settings.

For example, a Spanish multicenter, prospective, randomized, double-blind, controlled trial compared Dipeptiven®(0.5g/kg/day) with an isonitrogenous control (0.6g/kg/day) as a supplement in a TPN infusion in 132 ICU patients (Grau et al.,2011). The treatment was infused for 5-9 days continuously. The Dipeptiven® group had significantly less rates of pneumonia, nosocomial and urinary tract infections. Decreases in insulin needs were also seen in the Dipeptiven® group.

Similarly, a French multicenter, prospective, randomized, double-blind trial also compared Dipeptiven(0.5g/kg/day) with an isonitrogenous control(0.7g/kg/day) in 114 ICU patients with an indication for TPN over 5 days (Dechelotte et al., 2006). This study also resulted in significantly less infection and better metabolic tolerance in the Dipeptiven® group when compared to the isonitrogenous control group. In both studies, no toxicity was reported.

The Australian GLINT study (Al Balushi et al., 2011) was a phase 3, randomized, double blind, placebo-controlled study to investigate if intravenous glutamine supplementation to trauma patients improves outcomes of decreased organ dysfunction and infection. This study compared Dipeptiven, administered by intravenous infusion at a dose of 0.5g/kg/day, to a placebo intravenous infusion, both running 24 hours/day. These infusions were administered for

a maximum of 3 weeks. There are no results available at this time. The study was authorized May 2012 and is registered on *ClinicalTrials.*gov under identifier number NCT01240291.

With regard to its utility in applications involving the peritoneum specifically, alanyl-glutamine has been evaluated clinically for its ability to support and protect peritoneal tissues in cases of peritoneal disease, injury or insult. For example, alanyl-glutamine has been shown to reduce infectious complications by approximately 67% in patients with secondary peritonitis following surgery (Fuentes-Orozco, Clin Nutr 2004).

More recently, Aufricht and collaborators at the Medical University, Vienna, Austria, have undertaken a Phase II, randomized, open label study to evaluate the safety and tolerability of the addition of alanyl-glutamine-dipeptide to dialysis solutions in Peritoneal Dialysis (PD) patients. The study will evaluate the hypothesis that supplementation of PDF with pharmacological doses of alanyl-glutamine restores and increases the resistance of mesothelial cells to the injurious effects of dialysis fluid and preserves peritoneal integrity, as suggested by preliminary studies in vitro. The Aufricht study (EudraCT Number 2012-004004-36) was authorized on January 14, 2013 and is registered on *ClinicalTrials.gov.* No results for this study have been reported as yet.

The safety and tolerability of alanyl-glutamine is well established. In all cases of alanyl-glutamine evaluated thus far, reports of adverse effects associated with glutamine treatment in humans have been rare, and have been associated with chronic dosing regimens (> 2wks, 0.285 g/kg/day). For example, Hornsby Lewis, et al, 1994, did observe that glutamine in TPN infusions may cause hepatic toxicity, however, this effect was reversible upon termination of

glutamine treatment. The study involved 7 stable patients who received daily home TPN solutions supplemented with 0.285 g/kg of glutamine for four weeks. Five patients received the full 4 weeks of glutamine-TPN. In two patients, TPN infusions were stopped at the end of week 2 and 3 due to elevations in liver enzymes. Liver enzymes returned to normal range with the discontinuation of the glutamine supplementation. While the investigators cautioned against the use of glutamine on home TPN treatment, further evaluation is needed.

6.3 *Marketing Experience*

L-Alanyl-L-Glutamine has no market experience as a therapeutic. It is commonly used as a parenteral and enteral nutrition supplement.

7.0 Summary of Data and Guidance for the Investigator

L-Alanyl-L-Glutamine is a dipeptide of two naturally occurring amino acids. In the body, it is hydrolyzed to alanine and glutamine. Glutamine has been shown clinically to have cytoprotective effects in general, and in vitro studies have suggested that it boosts the cellular stress response in mesothelial cells of the peritoneum exposed to peritoneal dialysis fluid in patients with renal failure. As described in the foregoing, its application as an adhesion reduction agent dosed as a bolus intraperitoneal injection of 1g/Kg body weight at the time of surgery will be a new indication. Support for the efficacy of L-Alanyl-L-Glutamine for this indication has been derived directly from studies in the rat model conducted by A. Obayan at the University of Saskatchewan and indirectly from recent work by Aufrect and Kratochwill and coworkers involving the protection and support of mesothelial tissues during peritoneal dialysis.

L-Alanyl-L-glutamine, which has improved aqueous stability over glutamine alone, has a long history of safe and effective use in Total Parenteral and Enteral Nutrition in various clinical settings. Alanyl-glutamine is available commercially as the approved product, Dipeptiven®, manufactured by Fresenius Kabi. The Dipeptiven® formulation is an aqueous formulation similar to that of AdeTherapeutic's alanyl-glutamine test product. Studies reported in the literature to date, involving humans and animals and doses up to 1.5 mg/Kg body weight (rats), have shown no significant side effects or persistent adverse events at any dose studied Alanyl-glutamine has a relatively rapid elimination half life and clearance rate. At 0.3 mg/kg body weight bolus intravenous injection, the reported elimination half-life was 12 ± 2 min for initial slope and 67 ± 11 min for terminal slope, with a clearance rate of 2.3 ± 0.5 mg/kg/min, with little to no observed toxicity (Ziegler, 1990).

For the purpose of this trial, L-Alanyl-L-Glutamine will be dosed at 1g/kg of body weight. This dose not only falls within the range of approved parenterally infused commercial products such as Frasenius Kabi's Dipeptiven®, but is also consistent with No Observed [adverse] Effects Levels established in numerous controlled studies in humans and animals reported in the scientific literature.

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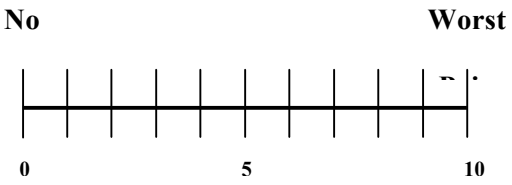
1009-16

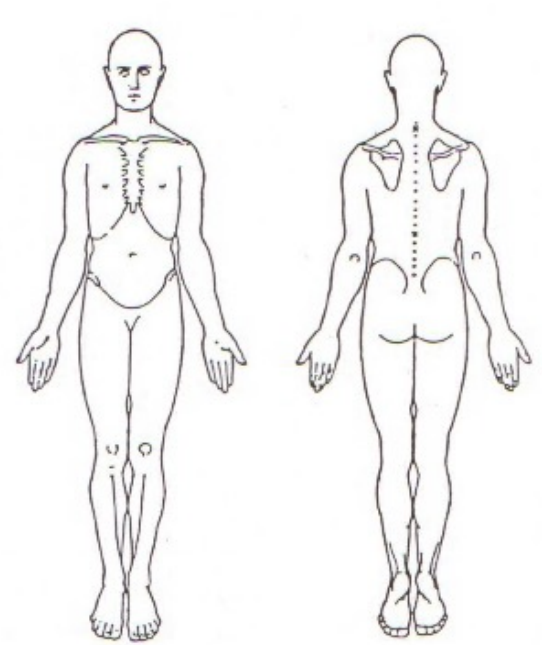
Please rate your pain using the scale below



Please answer the following questions related to your pain

QUESTION	ANSWER
What triggers your pain?	
How long does it last?	
How often do you experience this pain?	
What makes it better?	
What makes it worse?	
What does it feel like? Please describe.	
What part(s) of your body is the pain?	
Does your pain trigger any other symptoms (i.e. headache)	

Please mark with an x where you experience pain



Please list any medication you have taken for pain (name & amount):

_____

_____

_____

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_____

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_____

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_____

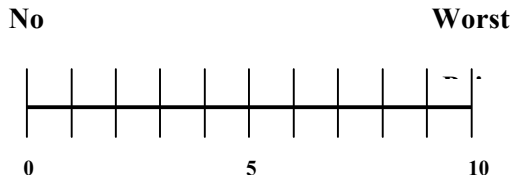
1.1 Adhesion Prevention in Myomectomy Study

Subject ID: _____

Subject Initials: _____

Date of Initial Surgery:

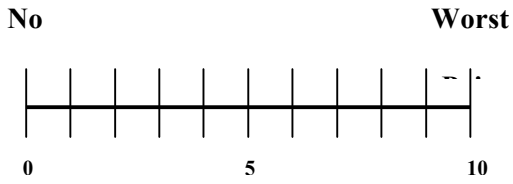
Please rate your pain using the scale below



Please answer the following questions related to your pain

QUESTION	ANSWER
What triggers your pain?	
How long does it last?	
How often do you experience this pain?	
What makes it better?	
What makes it worse?	
What does it feel like? Please describe.	
What part(s) of your body is the pain?	
Does your pain trigger any other symptoms (i.e. headache)	

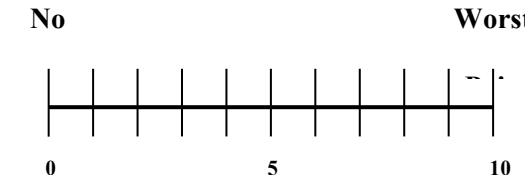
Please rate your pain using the scale below



Please answer the following questions related to your pain

QUESTION	ANSWER
What triggers your pain?	
How long does it last?	
How often do you experience this pain?	
What makes it better?	
What makes it worse?	
What does it feel like? Please describe.	
What part(s) of your body is the pain?	
Does your pain trigger any other symptoms (i.e. headache)	

Please rate your pain using the scale below



Please answer the following questions related to your pain

QUESTION	ANSWER
What triggers your pain?	
How long does it last?	
How often do you experience this pain?	
What makes it better?	
What makes it worse?	
What does it feel like? Please describe.	
What part(s) of your body is the pain?	
Does your pain trigger any other symptoms (i.e. headache)	

Title	**Standard Operating Procedure (SOP)** **Laparoscopic Myomectomy**
SOP Code	
No. of Pages	4
Effective Date	

Site Approval

Name and Title of Local Personnel	Signature	Date dd/Mon/yyyy

1.0 Purpose

This Standard Operating Procedure (SOP) describes the surgical process of a laparoscopic myomectomy for the removal of uterine fibroids.

2.0 Scope

This SOP pertains to all personnel conducting the laparoscopic myomectomy for the remov uterine fibroids.

Responsibilities

The Principle Investigator (PI) is responsible for performing his/her role, as described in this document.

The Gynecological Surgeon is responsible for performing his/her role, as described in this document.

The Anesthesiologist is responsible for performing his/her role, as described in this document.

Nursing staff is responsible for performing his/her roles, as described in this document.

Operation room technical staff is responsible for performing his/her roles, as described in this document.

3.0 Procedures

3.1 Pre-Operative

3.1.1 **The surgeon discusses the laparoscopic myomectomy procedure with the patient. The surgeon must insure that the patient is competent and understands both the surgery and the risks associated with the surgery. At this time the surgeon must inquire and respond to any questions or concerns the patient might have.**

3.1.2 **Patient signs the *consent for surgery* form in the presence of the physician or his/her designate.**

3.1.3 **Patient is admitted into the preoperative holding area**

3.1.4 **The anesthesiologist discusses the general anesthesia procedure with the patient.**

3.1.4.1 The anesthesiologist must insure that the patient is competent and understands both the procedure and the risks of anesthetic.

3.1.4.2 The anesthesiologist may perform a physical examination as required to ensure safe induction of anesthesia.

3.2 Operative

3.2.1 **The patient is brought into the operating room and lies on the operating table in a supine position.**

3.2.2 **The anesthesiologist places the patient under general anesthesia and continues to monitor the patient throughout the procedure.**

3.2.3 **The patient is placed in lithotomy position using Allen stirrups.**

3.2.4 **The patient's urinary bladder is catheterized using an indwelling Foley catheter.**

3.2.5 **The patient's skin is prepared for the surgery using current standard operating room procedures.**

3.2.6 **Sterile laparoscopy drapes are placed over the patient.**

3.2.7 **The 10mm 0 degree laparoscope and video camera with camera drape, CO_2 insufflation tubing, cautery cord and Nezhat or equivalent suction-irrigator equipped with saline are placed on the drapes.**

3.2.8 **A weighted speculum is placed in the vagina and a vaginal retractor is used to assist in the placement of the cervical tenaculum and canula. The retractor and speculum are removed.**

3.2.9 **A small intraumbilical incision is made.**

3.2.10 **The insufflator is set to a flow of 3 - 10 L/min and the carbon dioxide (CO2) is flowing.**

3.2.11 **The spring of the needle is assessed to ensure that the dull inner trocar can spring forward when it is released. The Verres needle is attached to the carbon dioxide tubing. The Verres needle is inserted through the subumbilical incision. The CO2 pressure is monitored during entry of the Verres needle, watching for a drop to <8mm, indicating intraperitoneal position.**

3.2.12 **The carbon dioxide is insufflated until a pressure of 25mm is reached, independent of the volume.**

3.2.13 **A visual entry system is used, if available, with an Ethicon blunt 10mm trocar and sleeve. The laparoscope is loaded into the trocar allowing for a visual entry through the umbilical port until the trocar is placed in the abdominal cavity. Alternately a 10mm trocar and sleeve is inserted blindly. The trocar is removed and replaced by the laparoscope.**

3.2.14 **The patient is placed in Trendelenberg position for the remainder of the operative procedure.**

3.2.15 **The 5 mm ports are placed under direct vision as needed. Ports may be positioned suprapubically or laterally, superior to the anterior superior iliac spine, or alternate postion as required for access to the pelvic anatomy, in an avascular plane as inspected with the laparoscope.**

3.2.16 **The pelvis is inspected to identify the uterine fibroids**

3.2.17 **Once the site of the uterine fibroid is in view, vasopressin diluted with saline, 10 units in 20 ml saline, is injected into the myoma, in the area where the myomectomy incision will be made. An incision is made with needlepoint cautery. Bleeding from the margin is controlled with cauterization.**

Fibroids are placed in a laparoscopic pouch and morcellation of the fibroid is completed to facilitate removal from the abdominal cavity. As required, intramyometrial sutures may be placed to reapproximate the edges of the remaining uterine muscle.

The edges of the uterine serosa may be reapproximated by using continuous running suturing technique or by interrupted mattress sutures.

The irrigation fluid is used to rinse the operative field to ensure hemostasis and removal of blood/debris around the reproductive organs.

3.2.18 **Excess peritoneal fluid may be removed from the pelvis and abdominal cavity. This may be aided by placing the patient in a supine position, aspirating fluid and reassuming Trendelenberg position to allow for inspection of the operative field prior to completion of surgery.**

3.2.19 **The CO_2 gas is expelled from the abdominal cavity through the 5 mm port. The laparoscopic tools are removed from the peritoneal cavity and the incisions are closed with interrupted or subcuticular sutures.**

3.2.20 **A simple dressing or transparent adhesive spray barrier is placed overtop of the sutured incisions.**

3.2.21 **The patient is placed in a supine position. Operative drapes are removed and replaced with covers. The patient is awakened from general anesthesia and transferred to a stretcher.**

3.2.22 **The patient is taken to the postoperative care unit (PACU) to be monitored as she wakes and recover from the general anesthesia.**

3.3 Postoperative

3.3.1 **The patient is transferred from the PACU to a surgical unit to be further monitored, educated and managed.**

4.0 References

Boyd, M.E. (1990). **Practical Gynecologic Surgery**. Urban & Schwarzenberg: Munich.

5.0 Revision History

Title	**Standard Operating Procedure (SOP)** **Laparotomy and Myomectomy**
SOP Code	
No. of Pages	4
Effective Date	

Site Approval

Name and Title of Local Personnel	Signature	Date dd/Mon/yyyy

6.0 Purpose

This Standard Operating Procedure (SOP) describes the surgical process of a laparotomy and myomectomy for the removal of uterine fibroids.

7.0 Scope

This SOP pertains to all personnel conducting the laparotomy and myomectomy for the removal of uterine fibroids.

Responsibilities

The Principle Investigator (PI) is responsible for performing his/her role, as described in this document.

The Gynecological Surgeon is responsible for performing his/her role, as described in this document.

The Anesthesiologist is responsible for performing his/her role, as described in this document.

Nursing staff is responsible for performing his/her roles, as described in this document.

Operation room technical staff is responsible for performing his/her roles, as described in this document.

8.0 Procedures

8.1 Pre-Operative

8.1.1 **The surgeon discusses the myomectomy procedure done at laparotomy with the patient. The surgeon must insure that the patient is competent and understands both the surgery and the risks associated with the surgery. At this time the surgeon must inquire and respond to any questions or concerns the patient might have.**

8.1.2 **Patient signs the *consent for surgery* form in the presence of the physician or his/her designate.**

8.1.3 **Patient is admitted into the preoperative holding area**

8.1.4 **The anesthesiologist discusses the general anesthesia procedure with the patient.**

8.1.4.1 The anesthesiologist must insure that the patient is competent and understands both the procedure and the risks of anesthetic.

8.1.4.2 The anesthesiologist may perform a physical examination as required to ensure safe induction of anesthesia.

8.2 Operative

8.2.1 **The patient is brought into the operating room and lies on the operating table in a supine position.**

8.2.2 **The anesthesiologist places the patient under general anesthesia and continues to monitor the patient throughout the procedure.**

8.2.3 **The patient's urinary bladder is catheterized using an indwelling Foley catheter.**

8.2.4 **The patient's skin is prepared for the surgery using current standard operating room procedures.**

8.2.5 **Sterile laparotomy drapes are placed over the patient.**

8.2.6 **An abdominal incision is made as a pfannensteil or midline abdominal subumbilical and carried through the abdominal wall layers: skin, subcutaneous tissue, fascia, peritoneum as per standard protocol. Muscle incision is avoided by retracting rectus muscles laterally during entry into the peritoneal cavity.**

8.2.7 **The insufflator is set to a flow of 3 - 10 L/min and the carbon dioxide (CO2) is flowing.**

8.2.8 **The uterus is inspected to identify the position of the uterine fibroids.**

8.2.9 **Once the site of the uterine fibroid(s) is (are) in view, care is taken to determine the best incision site for myomectomy that will decrease the potential for obstruction of**

the uterine interstitium and that will allow excision of the maximum number of fibroids from one incision.

8.2.10 **Vasopressin diluted with saline, 10 units in 20 ml saline, may be injected into the myoma, in the area where the myomectomy incision will be made to decrease blood loss.**

8.2.11 **The incision through the uterine serosa is made with needlepoint cautery. Bleeding from the margin is controlled with cauterization.**

8.2.12 **The incision is carried through the myometrium until the myoma can be identified and cored out (excised) from the normal myometrial tissue.**

8.2.13 **As required, intramyometrial sutures may be placed to reapproximate the edges of the remaining uterine muscle.**

8.2.14 **The edges of the uterine serosa are reapproximated by using continuous running suturing technique with a non-braided absorbable suture (preferably 5-0 or finer gauge) or a non-absorbable suture.**

8.2.15 **The irrigation fluid is used to rinse the operative field to ensure hemostasis and removal of blood/debris around the reproductive organs. Excess peritoneal irrigation fluid is removed from the pelvis and abdominal cavity.**

8.2.16 **The abdominal wall incision is closed in separate layers to reapproximate the peritoneum, fascia, subcutaneous tissue, and skin. Subcutaneous running/continuous or intermittent skin sutures or staples may be used to close the skin.**

8.2.17 **A simple dressing is placed on the sutured incisions.**

8.2.18 **Operative drapes are removed and replaced with covers. The patient is awakened from general anesthesia and transferred to a stretcher.**

8.2.19 **The patient is taken to the postoperative care unit (PACU) to be monitored as she wakes and recover from the general anesthesia.**

8.3 Postoperative

8.3.1 **The patient is transferred from the PACU to a surgical ward to be further monitored, educated and managed.**

9.0 References

Boyd, M.E. (1990). **Practical Gynecologic Surgery**. Urban & Schwarzenberg: Munich.

10.0 Revision History

**Gnrh agonist – protocol????

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29 February 2012

Dr. Gordon McKay, Chair
Biomedical Research Ethics Board
University of Saskatchewan
1607 - 110 Gymnasium Place
Saskatoon, Saskatchewan
S7N 0W9

Dear Dr. McKay:

We am writing to provide full disclosure of a relatively unusual situation involving a clinical trial now initializing in the Department of Obstetrics, Gynecology and Reproductive Sciences and a graduate student who is working towards her MSc degree under our supervision.

The trial is Protocol Number ADE001 entitled *A Randomized, Double-Blind, Placebo Controlled Phase I Study of the Efficacy and Safety of L-Alanyl-L-Glutamine For the Reduction of Peritoneal Adhesions in Adult Females Undergoing a Laparoscopic Salpingostomy for the Removal of an Ectopic Pregnancy.* The Principal Investigator is Dr. Donna Chizen. The President and CEO of ADE Therapeutics, Incorporated is Mr. Sanjeev Singh. ADE Therapeutics is a startup pharmaceutical company located in Saskatoon that is funding the research.

We need to make the University of Saskatchewan Biomedical Research Ethics Board and the Saskatoon Centre for Patient Oriented Research aware that our graduate student, Dominique Chandra Singh RN, is the daughter of Mr. Sanjeev Singh. We wish to assure you and the University REB that in her role as a graduate student, Dominique will not be involved in any aspect of retention of participants in the trial independently of the PI. If a participant voices concerns about their continuing participation in the trial, Dr. Chizen will communicate with the individual and their attending physician.

ADE has a unique product that we are going to administer when ectopic pregnancies are surgically removed to ameliorate the surgical damage to the oviduct. It is important for us to be able to do the initial work in the gynecological surgery arena in Saskatoon and to set the precedent for its potential use world-wide. The trial is double blinded and the PI and the research team will not know the identity of the real versus placebo nutriceutical agent. We will receive the agent and placebo vials directly from the manufacturing plant and the code identifying each vial is sealed. We expect to perform an interim analysis during the trial for safety reasons as requested by the University of Saskatchewan IRB. Neither the Research Team, nor ADE Therapeutics, will know the identity of active versus placebo products prior to the time the code is broken for interim analyses and final study closure.

All clinical trials in the Department of Obstetrics, Gynecology and Reproductive Sciences are conducted in full compliance with the Declaration of Helsinki, the Canadian Tri-Council Statement for Research Involving Humans, Health Canada, and ICH Good Clinical Practice Guidelines. We have extensive experience in the design, performance and analysis of national and international clinical trials and are quite proud of our record of achievement. We will conduct the present trial to the exceptionally high standard that we have developed and look forward to its successful implementation. As always, our facilities and trials are open to University of Saskatchewan audit procedures. You and any members of the University of Saskatchewan IBR or the Saskatoon Centre for Patient Oriented Research are always welcome in our laboratory.

If we may provide any additional information, please do not hesitate to contact either of us directly. Dr. Chizen and Dr. Pierson are available at the phone numbers identified on the letterhead. Our electronic mail addresses are donna.chizen@usask.ca and pierson@erato.usask.ca, respectively.

Sincerely,

Donna R. Chizen, MD FRCSC
Associate Professor

Roger A. Pierson, MS PhD FEAS FCAHS
Professor and Director of Research

Cc: Dr. T. Mainprize, Chair, Obstetrics, Gynecology and Reproductive Sciences