## Table of Contents

OVERVIEW ................................................................................................................................. 02

CLINICAL OVERVIEW ............................................................................................................... 04

SERVICES

- Project Management Experts ......................................................... 03
- Rapid Recruiting ................................................................. 07
- Special Populations ................................................................. 07
- Streamlined Operations ................................................................. 08
- Regulatory Services ................................................................. 08
- First-in-Man ................................................................. 09
- Proof-of-Concept ................................................................. 09
- QT/TQT ................................................................................. 10
- Bioavailability/Bioequivalence .......................................................... 10
- Biosimilars ................................................................................. 10
- Drug-Drug Interaction ................................................................. 10
- Validated Assays ................................................................................. 10
- Data Management Services ................................................................. 10
- Conducting Phase I Clinical Trials In Canada ................................. 13
Overview

OUR PHASE I-IIA SERVICES
At inVentiv Health Clinical we have the ability to expedite clinical programs and build the foundation for continued development of the product. With more than 15 years of experience, we provide our sponsors with the appropriate talent, experience, processes and infrastructure to successfully conduct your clinical study. We offer a full range of services, from protocol development to report preparation, to help sponsors reduce costs, shorten timelines and achieve quality data.

DIVERSE EXPERIENCE
Our broad exposure to different types of studies, therapeutic areas and dosage forms allows us to develop a creative and innovative design for studies, including first-in-man, proof-of-concept, drug-drug interaction, single ascending dose/multiple ascending dose (SAD/MAD) and cardiac safety.

OUTSTANDING PROJECT MANAGEMENT
A dedicated project manager is assigned to each study, supported by a team of experts, including physicians and specialists in patient recruitment, clinical operations, quality assurance, biostatistics and clinical pharmacology. These experts work with sponsors to minimize risks and establish contingency plans, providing robust quality and regulatory controls to ensure protocol compliance and patient safety.

EXPEDITED PHASE I STUDIES
Strategic hospital partnerships and an extensive centralized database give us broad access to a significant population of potential participants, including special populations. This, along with our ability to develop efficient processes in all study areas, means we can effectively expedite the conduct of any study, regardless of its size or complexity. Advanced technology, including Initiator™ software, expedites studies and provides real-time data. All departments and business processes comply with current GLP, GCP and ICH standards, while an independent quality assurance unit validates study data and reports, providing the basis for our exceptional regulatory success.

inVentiv Health Clinical’s extensive experience, streamlined processes and state-of-the-art facilities can help mitigate risk in your Phase I–IIa programs. It’s just one more way inVentiv Health Clinical is transforming promising ideas into commercial reality.
inVentiv Health Clinical has conducted thousands of studies and typically files more than 180 clinical trial applications annually. With broad experience in a variety of study types, therapeutic areas and dosage forms, our team has the expertise to conduct early stage studies that meet your specific requirements.

DIVERSE EXPERIENCE

- Study types
  - Age/gender
  - Bioavailability
  - Bioequivalence
  - First-in-man
  - Food/drug interactions
  - Genotyping
  - Medical devices
  - New dosage forms
  - PK/PD
  - Safety/tolerability
  - Vaccines

- Administration
  - Inhalation
  - Injectable (IV, IM, SC)
  - Oral
  - Rectal
  - Patch/dermal

THERAPEUTIC INDICATIONS
Clinical Overview

inVentiv Health Clinical conducts Phase I–IIa clinical trials at its dedicated 22,000-square-foot clinical facility comprising more than 200 beds in four independent units. Experienced on-site physicians and medical professionals are available to ensure the safety of participants. Integrated clinical operations, expert project managers and skilled statisticians ensure a professionally executed study. Once your clinical trial has started, our clinical laboratory can perform all the necessary safety assessments to support your study.

QUALITY ASSURANCE
Providing robust quality and regulatory controls throughout the entire study will promote compliance. inVentiv Health Clinical’s quality assurance processes help ensure the success of every study. Some of these processes include conducting internal training programs, auditing vendors, validating software and establishing SOPs. In addition, all of our business processes are GLP-, GCP- and/or ICH-compliant. Our facilities have been successfully audited by major regulatory agencies, including the FDA, EMA, Health Canada and several European agencies.

CLINIC FEATURES
- Modern, purpose-designed facility
- Safe and secure environment
- Semi-private rooms, maximum of eight participants per room
- Controlled access and stringent control of the facility and drug products to ensure patient safety
- GLP-, GCP- and/or ICH-compliant processes
- Less than 10 minutes from local hospitals
- Minutes from Jean-Lesage International Airport
SAFE DRUG HANDLING

inVentiv Health Clinical offers an on-site, state-of-the-art pharmacy that provides a range of delivery methods and special storage conditions, including those required for controlled substances. Storage of your drug product is controlled by a medication team comprised of a pharmacist and medication technicians who also assist with dispensing tablets and capsules, preparation of suspensions and filling of syringes. Dose preparation and drug dispensing is performed under aseptic conditions, including IV bolus, IV infusion, subcutaneous and intramuscular.

Dosage form preparation and dispensing is tightly controlled and monitored, with measures including:

• Limited restricted access
• Monitoring by a security alarm system 24/7
• Temperature and humidity controls (15–25°C and 30–60% H)
• Licensed for controlled drugs
• Laminar flow hoods for aseptic preparation techniques
• Ambient, refrigerated, -20°C and -80°C storage capabilities
## Services

### PROJECT MANAGEMENT EXPERTS

A knowledgeable team of professionals in business development, clinical operations, medical affairs and clinical pharmacology is central to mitigating risk in clinical studies. At inVentiv Health Clinical, our project management team ensures the study will be executed on time and within the scope of the study requirements. Our project managers work with sponsors and other inVentiv Health Clinical team members to schedule the necessary resources, resolve issues and manage critical milestones to ensure the project stays on track, on budget and on time.

Our clinical operations team includes a wide range of medical professionals, such as doctors, nurses, medical technicians and clinical project coordinators to provide the safest environment for the study participants during the trial. inVentiv Health Clinical also provides access to experienced staff in cardiac safety and drug interactions for more complex trials.

Scientific and regulatory affairs experts are available to collaborate throughout the study in the assessment of overall feasibility, protocol development, bioanalytical and clinical feasibility, recruitment planning and screening, institutional review board presentation and regulatory submission.

### ACCESS TO COMPREHENSIVE RESOURCES

<table>
<thead>
<tr>
<th>PROJECT MANAGER</th>
<th>CLINICAL OPERATIONS</th>
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<tbody>
<tr>
<td>• Primary point of contact:</td>
<td>• Participant/patient recruitment and screening</td>
</tr>
<tr>
<td>- Ensures expectations are met</td>
<td>- Monitor study</td>
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<td>- Timely communication and reporting</td>
<td>- Ensure participant safety</td>
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<td>• On-site physicians and medical professionals</td>
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<td>- Monitor study</td>
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<tr>
<th>CLINICAL PHARMACOLOGY</th>
<th>QA AND IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Protocol</td>
<td>• Support services</td>
</tr>
<tr>
<td>• Regulatory submission</td>
<td>- Deliverables meet specifications</td>
</tr>
<tr>
<td>• Biostatistics and pharmacometrics</td>
<td></td>
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<tr>
<td>• Data management</td>
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<td>• Medical writing</td>
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<th>QA AND IT</th>
<th>SPONSOR</th>
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<td>• Support services</td>
<td>• Deliverables meet specifications</td>
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**SPONSOR**
RAPID RECRUITING
inVentiv Health Clinical's comprehensive recruiting center has access to an extensive database of participants for client studies. A centralized database allows sites to rapidly access potential participants who may meet the specific study requirements. The inVentiv Health Clinical database also mitigates the risk of a participant joining in multiple studies simultaneously. The database has a good refresh rate and a favorable mix of new and repeat participants. It can accommodate requests for different groups segmented by age, gender, smoking habit, and healthy or special populations.

For more complex studies, we have the ability to employ a number of recruitment strategies. From traditional print ads to social media, we have experience executing marketing initiatives to ensure we rapidly fill study panels. In addition, we have successfully launched online incentive programs that have expanded access to healthy participants and special populations.

SPECIAL POPULATIONS
Our extensive centralized database and strategic partnerships with local hospitals enable us to access a significant population of potential participants, which is critical to a successful recruitment process. We offer sponsors access to a diverse group of both healthy participants and special populations.

OUR WIDE RANGE OF SPECIAL POPULATIONS INCLUDES:
- Asthma
- Cardiovascular disease
- Chronic obstructive pulmonary disease
- Diabetes
- Gastrointestinal diseases
  - Peptic ulcer disease (PUD) and/or gastroesophageal reflux disease (GERD)
- Geriatrics
- Hyperlipidemia
- Hypertension
- Hypogonadism
- Metabolic disorders
  - Extensive/poor metabolizers
- Obesity
- Renally impaired
- Women's health-related conditions
  - Healthy premenopausal women with regular menstrual cycles with and without oral contraceptives
  - Surgically sterile females
  - Postmenopausal women
STREAMLINED OPERATIONS
Effective study design starts with the development of a protocol that includes all of the study parameters, and focuses on improved study efficiency. inVentiv Health Clinical’s Phase I–IIa experts in all areas of our operations can help develop the initial protocol. We work with sponsors to develop creative and innovative study designs for first-in-man, proof-of-concept, drug drug interaction, SAD/MAD and cardiac studies, ensuring streamlined execution for every study.

In addition, our operations team consults with sponsors who provide their own study design. We conduct a thorough feasibility study and assess inclusion/exclusion criteria to ensure successful program execution and patient safety. We build a project plan to make certain we meet all critical milestones.

inVentiv Health Clinical’s e-source data capture system, Initiator™ CTMS, reduces data verification time, the possibility of errors and eliminates the need for data transcription onto Case Report Forms. The system is specifically designed for Phase I clinical trials and allows for rapid study set-up (a standard study can be set up in a matter of hours). Front end checks that are incorporated directly into e-source data capture include time and range tolerances, required fields and response-driven fields. The use of data/time stamps, medical instrument interfaces and study-specific code lists further reduces the possibility of source data errors. Bar codes for identification of subjects, study medications, collected samples, processed samples and instruments ensure seamless tracking and data reliability. Our CTMS provides real-time access to accurate data, and ensures source data integrity and improved study timelines.

REGULATORY SERVICES
Changing regulations promoted by global regulatory agencies represent a complex and ever-changing environment. To help you navigate successfully, inVentiv Health Clinical has assembled an exceptional team of former senior-level FDA and EMA officials, in addition to other international regulatory and pharmaceutical experts. inVentiv Health Clinical’s generic drug development service list includes:

- Study design and protocol development
- Medical writing
- Consulting
- Regulatory submissions
- 505(b)(2) support services

Expedited Regulatory Submissions
inVentiv Health Clinical typically files more than 180 clinical trial applications annually. Our high volume of work, along with our lengthy relationships with these agencies, facilitates rapid study approval. During the last three years, the average review time for bioequivalence studies was six days, and the average review time for Phase I studies was just 20 days.
**FIRST-IN-MAN**

First-in-man clinical trials require detailed preparation and care, recognition of ethical and safety responsibilities to study participants, and a deep understanding of the critical role these tests play in moving a compound forward. inVentiv Health Clinical's experience, specialized operational teams, attention to detail and access to special populations ensure a smooth transition into ascending dose studies. Drug concentrations and biomarkers of interest can be measured on site in our bioanalytical laboratories and integrated into study reports.

We have extensive experience in both small molecules and biological compounds, and have the capability to manage all aspects of the study process. Our team also executes combination study designs, such as SAD/MAD, as a means to reach proof-of-concept faster, safer and more economically. Our in-house bioanalytical capabilities provide timely dose escalation information based on safety and PK data.

**PROOF-OF-CONCEPT**

Proof of concept studies explore the relationship between the dose and desired outcome, and establish the safety of drug candidates in the target population. Our scientific team works closely with you to design proof-of-concept studies to reduce risk and avoid costly late-stage clinical development failures. In addition, because of our knowledge across a wide range of therapeutic indications and our collaborations with local hospitals, inVentiv Health Clinical can provide sponsors with enhanced access to study participants with special conditions and diseases.

**QT/TQT**

inVentiv Health Clinical conducts investigational drug studies to assess risk as early as possible and evaluate the drug’s effect on the cardiovascular system. QT/TQT studies are conducted at our own facility, which comprises 200 beds in four distinct clinical units that can be combined to accommodate large cohorts. An experienced team of medically trained staff and nurses supports each study.

inVentiv Health Clinical maintains close relationships with ECG core laboratories and can monitor as many as 49 participants simultaneously on its cardiac telemetry system, which is an ideal use of technology for first-in-man studies of drug candidates with potential cardiac liability.

**BIOAVAILABILITY/BIOEQUIVALENCE**

inVentiv Health Clinical’s significant experience in conducting a full range of bioavailability and bioequivalence clinical trials has given us a thorough understanding of the generic development process. You can have confidence that your project will be completed professionally and on time.
BIOSIMILARS
Opportunities are also increasing for follow-on biologicals or biosimilars despite the unique complexity of demonstrating similarity of efficacy and safety, and the evolving regulatory landscape. inVentiv Health Clinical experts work with sponsors to develop a clinical development program for biosimilar products that include such strategies as comparability protocols. Our large capacity means that we can be ready when you are, including assessing the performance in special populations.

DRUG DRUG INTERACTION
As required by regulatory agencies, how an investigational drug is metabolized must be defined during early drug development, and its interaction with other drugs must be explored, as part of an adequate assessment of safety and effectiveness.

inVentiv Health Clinical professionals evaluate the safety profile of the compound under co-administration regimes while ensuring the well-being of study participants. Because not every drug drug interaction is metabolism-based but may arise from changes in pharmacokinetics caused by absorption, distribution and excretion interactions, inVentiv Health Clinical offers a full range of studies, including the evaluation of pharmacodynamic effects.

505(B)(2) CONSULTING SERVICES
inVentiv Health Clinical provides comprehensive support services to help you navigate the 505(b)(2) regulatory pathway. Whether you are considering brand extensions, new indications, formulations, active ingredients (e.g., new salt), dosage forms or a combination of new entities, inVentiv Health Clinical has the strategic and scientific expertise to help you develop and introduce new and improved products, and invigorate your brands.

INVENTIV HEALTH CLINICAL’S DRUG DEVELOPMENT SERVICES INCLUDE:
- Bioanalytics
- Medical writing
- Pharmacokinetics
- Protocol development
- Study conduct
- Data management
**VALIDATED ASSAYS FOR COMPOUNDS WITH POTENTIAL DRUG-INTERACTION OR CO-ADMINISTRATION STUDIES**

**MISCELLANEOUS**
- digoxin
- docetaxel
- enalaprilat
- erlotinib
- escitalopram
- ethinyl estradiol
- ezetimibe
- fluvoxamine
- gemfibrozil
- glyburide
- hydrochlorothiazide levonorgestrel
- levothyroxine metformin
- moxifloxin
- norethindrone
- norgestimate
- oxybutynin
- paclitaxel
- pioglitazone repaglinide rosvastatin tolterodine

**2C9**
- NSAIDs
diclofenac
ibuprofen

**ORAL HYPOGLYCEMIC AGENTS**
glipizide

**ANGIOTENSIN II BLOCKERS**
irbesartan
losartan

**MISCELLANEOUS**
celecoxib
fluvastatin
phenytoin
tamoxifen
torsemide
warfarin

**2C19**

**2C19**

**PROTON PUMP INHIBITORS**
lansoprazole
omeprazole
pantoprazole
rabeprazole

**ANTIDEPRESSANTS**
desipramine (m)
paroxetine
venlafaxine

**ANTIPSYCHOTICS**
aripiprazole
haloperidol
risperidone

**ANTITUSSIVE**
dextromethorphan (m)
dextorphan

**MISCELLANEOUS**
codeine
ondansetron
tamoxifen
tramadol

**2E1**

**MACROLINE ANTIBIOTICS**
clarithromycin
erythromycin

**HMG COA REDUCTASE INHIBITORS**
atorvastatin
lovastatin (m)
pravastatin
simvastatin (m)

**MISCELLANEOUS**
aripiprazole
buspirone (m)
haloperidol
diledoxifene

trazodone

**BENZODIAZEPINES**
alprazolam
diazepam
midazolam (m)

**IMMUNE MODULATORS**
cyclosporine
tacrolimus

**HIV PROTEASE INHIBITORS**
ritonavir

**CALCIUM CHANNEL BLOCKERS**
amiodpine
diltiazem
felodipine (m)
nifedipine
verapamil

**ANTIFUNGAL**

**ANTIHISTAMINES**
chlorpheniramine

**BETA BLOCKERS**
S-metoprolol

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**Notes**
1. Additional information on CYP enzyme systems can be found at [http://medicine.iupui.edu/flockhart/](http://medicine.iupui.edu/flockhart/)
2. Transporter information can be found at [http://125.206.112.67/tp-search/login.php](http://125.206.112.67/tp-search/login.php)
3. (m): model substrate for the CYP system listed recognized in the FDA guidance

**Additional References**
**Services**

**CLINICAL PHARMACOLOGY**
inVentiv Health Clinical’s clinical pharmacology team includes experts in PK, biostatistics, pharmacometrics and data management, backed up by experienced QA specialists. Working together with the sponsor, inVentiv Health Clinical analyzes the data using automated and validated systems for rapid compilation of the clinical study report.

**CLINICAL PHARMACOLOGY SERVICES**

- Biostatistics and Pharmacometrics
  - Bioequivalence/bioavailability studies
  - Phase I–IIa clinical trial
  - PK for preclinical studies (TK studies)
  - PKS (Pharsight Knowledge Server) to effectively and securely manage PK/PD data and association analyses
  - Derived dataset creation
  - Model fitting
  - Statistical analysis plan preparation and writing
  - TLFs programming

- Data Management
  - Medical coding
  - CRF design and mapping
  - Database design/build
  - Data review
  - Submission ready CDISC-compliant dataset production (SDTM and ADaM)

- Medical Writing
  - Clinical study reports and summaries
  - Investigator brochures
  - Participation to SAP
  - Safety, efficacy and PD data interpretation
CONDUCTING PHASE I CLINICAL TRIALS IN CANADA

Canada is a prime location for conducting innovative clinical research because it enables us to provide cost-effective solutions and the fast turnaround you need. Canada has a high-quality network of public and private clinical settings, a dependable and efficient clinical trial application (CTA) review process and large pools of potential participants.

Cost Effective
Canada offers one of the lowest business costs of any G-8 country for pharmaceutical, biomedical and medical device research. Companies with offices in Canada may also be able to receive favorable R&D tax credits.

Expedited Regulatory Process
Canada's competitive CTA process has a maximum review period of 30 days, except for bioequivalency studies in healthy participants, which have a targeted review time of seven days. inVentiv Health Clinical clinics typically achieve a 16- to 20-day turnaround for CTA review of Phase I studies in normal healthy participants; biologics typically take the full 30 days. Bioequivalency studies can take as few as five days.

Patient Safety and Data Integrity
inVentiv Health Clinical is a member of an inter-CRO data exchange of clinical trial participants. This exchange protects both study participants and data integrity by preventing simultaneous enrollment in multiple clinical trials and prevents us from selecting individuals before the washout interval has elapsed.

Expertise
Working with inVentiv Health Clinical on your Phase I–IIa clinical trials means you have the advantages of an experienced partner and a favorable regulatory environment. inVentiv Health Clinical has over 15 years of experience conducting Phase I and bioequivalence studies. We have expertise in early-stage clinical trial execution and solid project management, from protocol design to final study report preparation. Regulatory consultants at inVentiv Health Clinical's clinical facilities in Canada can assist in every aspect of early-stage drug development, including the submission of a CTA to Health Canada, the Canadian regulatory authority.