Strategies for clinical development planning
Sietsema and Brass

Clinical trials, good clinical practice, regulations, and compliance
Gaur et al.

Planning for a clinical trial application
Arora
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Published by

Regulatory Affairs Professionals Society
5635 Fishers Lane, Suite 400
Rockville, Maryland 20852, USA
Phone: +1-301-770-2920  Email: raps@raps.org

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Introduction: Global Clinical Trials

Welcome to the inaugural issue of RF Quarterly featuring original, thematically developed content by regulatory experts addressing key areas and emerging issues in the global regulatory landscape. RF Quarterly is a member-exclusive addition to the regular monthly Regulatory Focus feature articles and replaces the former quarterly article series. The theme for this issue is Global Clinical Trials.

Clinical trials are an essential component of pharmaceutical research and development. In recent years, clinical trials have become more global, and while they offer many advantages for patients and sponsors, the logistics and complexities of operating in a number of countries are challenging. In this issue, regulatory experts examine clinical development planning, the regulations and guidelines governing local and multiregional clinical trials, good clinical practice and compliance, and clinical trial applications. A cluster of articles also addresses the importance of innovation and adaptability in initiating and maintaining clinical trials. In addition to providing valuable context, the articles also have a strong “how-to” subtext, providing tools and resources for readers to draw on in daily, real-world regulatory practice. And as is often the case in regulatory practice, almost all the articles carry a cautionary message about staying up to date with the dynamic clinical and regulatory landscape.

I thank the authors for their generosity in sharing their knowledge and expertise with their regulatory colleagues.

Strategizing, planning, and compliance
Establishing an effective strategy for the clinical development of a new product requires striking a balance between research, strategic planning, and critical thinking. Clinical development is extremely costly, so the resulting plan should chart the quickest, most efficient pathway to successful global registration for the product, write William Sietsema and Eric Brass in Strategies for clinical development planning (p. 5). A key first step is to develop a vision for the product. The authors suggest starting with the target product profile and a supporting indication statement and then, using the reverse-engineering approach, refine the trial design and stages, define the patient population and measurable endpoints, and establish the statistical analysis plan. Most important, they caution, is to speak to regulators early and often to make sure regulatory needs and changes are addressed and factored in continuously.

Planning and conducting a clinical trial, whether in single or multiple regions, requires in-depth knowledge of international good clinical practice (GCP) and regional and national legislation, regulations, and guidances, write Anu Gaur, Bettina
Merz-Nideroest, and Andrea Zobel. In Clinical trials, good clinical practice, regulations, and compliance (p. 15), the authors provide an overview of the international and national guidelines for clinical trials and outline the principles of the International Council on Harmonisation (ICH) GCP Guideline and regulatory compliance. In addition, Gaur and colleagues provide invaluable resources for readers, including a user-friendly, in-depth glossary of commonly used definitions and terms relating to clinical trials, documentation, and quality and compliance. These authors echo Sietsema and Brass in advising continuous monitoring of the global and local regulatory landscapes and speedy adaptation to any regulatory changes along the trajectory of the trial.

Global, multiregional clinical trials have become more prevalent in recent years, offering a range of advantages, such as improved access to treatment-naive participants, a better opportunity for demonstrating the true impact of an investigational drug, and reducing trial costs in developing countries. Planning these trials has become more exacting and essential for successful trial initiation, management, and maintenance. In Planning for a clinical trial application (p. 33), Sharry Arora notes that the key considerations in designing a global clinical trial are selecting the most appropriate trial sites with a representative patient population, choosing to work with the right partners, and staying up-to-date with the changing regulatory and clinical landscape. She offers hands-on guidance on site selection; assembling a global dossier; product supply, labeling, and storage; document translations; amendments and updates; financial disclosures; and investigation records.

Keeping up with change

Since 2017, Health Canada has introduced a plan to modernize its clinical trial regulations to be more flexible and adaptive to change and innovations, such as artificial intelligence, advanced cell therapies, and 3D-printed bioproducts. In Modernizing clinical trial regulations in Canada (p. 40), Tanya Ramsamy provides an overview of these efforts to date and examines how clinical trials in several health care product lines can be modernized. Ramsamy looks at how lessons learned from the COVID-19 pandemic experience can help set up a more flexible regulatory framework better aligned with international standards and practices. She concludes that closer alignment with international, risk-based approaches and enabling novel clinical trial design will increase treatment options and product access for Canadians.

Canada is an attractive destination for conducting clinical trials, in part because of its shorter approval timelines and more universal submission requirements. In The Canadian application process and alternate pathway for COVID-19–related trials (p. 45), Mukesh Kumar and Melanie Oakley describe the clinical trial application process for biologics (schedule D) and pharmaceuticals (schedule F) and provide an overview of guidance on the regulatory obligations for clinical trials in humans under Part C, Division 5 of Canada’s Food and Drug Regulations. The authors also share useful information on clinical trial submission requirements, folder structure and transmission of data, the review and screening processes, communication with the relevant directorates and offices; and post-authorization requirements.

China-based clinical trials for medical device and in vitro diagnostic device products are an increasingly viable option for non-Chinese companies of all sizes, writes Hamish King in Initiating clinical trials in China: What foreign medtech companies need to do (p. 55). King discusses China’s regulatory framework and recent regulatory developments to align with international standards and outlines what foreign companies should consider before initiating a clinical trial in China.

Acknowledgment

I would like to thank the following colleagues for making this launch possible: Denise Fulton and Gloria Hall, for their editorial support and guidance; Art Director Simon Fong; Jennifer Zayas for production support; Amy Fisher and Aaron White for helping our members learn about this new product; Wendy Sahli and Ravi Gaddipati for website development; and freelance contributor Randolph Fillmore.
Upcoming issues
This year, RF Quarterly will address:
• Artificial Intelligence in Regulatory Affairs (June)
• Quality and Compliance in Regulatory Affairs (September)
• RAPS 2021 Convergence (December)

To contribute to the June issue of RF Quarterly or any upcoming issue, email rmatthews@raps.org.

For more information, see Guidelines for Authors and the 2021 Editorial Calendar.

About the author
Renée Matthews, Senior Editor, is responsible for RF Quarterly and Regulatory Focus feature articles. She can be contacted at rmatthews@raps.org.

If the regulatory affairs professional can anticipate certain regulatory requirement changes, understand how these changes may affect product performance in the regulatory environment (for both products under development and those approved), and communicate proactive strategies, they could potentially provide a competitive edge and ensure ongoing compliance.

Kirsten Messmer, Author, Chapters 4 and 18

With contributions from more than 30 authors from seven countries, the third edition of *Regulatory Intelligence 101* incorporates a global overview of the field. It’s designed to help you get the most out of your regulatory intelligence endeavors by relating the work to due diligence efforts, citing key agencies and explaining how they are organized, identifying metrics to help measure success, and providing a comprehensive guide to sources and databases.

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Strategies for clinical development planning

Clinical development planning can be thought of as the integrated design and structuring of the steps from the first phase 1 study for the initial assessment of safety, to one or more phase 2 studies for better understanding the product’s pharmacology, safety, and effectiveness, to a phase 3 definitive demonstration of efficacy and safety. Optimal strategy can be informed by creating a vision for the product in the form of a target product profile, examining precedence (where available), discussing important design elements with regulators, and creating a sequence of studies that delivers superior marketing claims while meeting regulator needs.

Developing a vision
Clinical development is a very expensive undertaking, so it is prudent to map out the most rapid and efficient pathway to successful global market registrations. Reverse engineering is one of the most effective ways to develop a robust plan that optimizes the product’s value.¹

A critical first step is to develop a vision for the product, consisting of specific indication statements similar to those that would be included in a package insert or summary of product characteristics.² Indication statements have a strong influence on clinical program design, particularly for patient populations and measurable endpoint selection, as well as the nature of the study’s statistical analysis plan.

Another important step in designing a superior development program is understanding both the regulatory environment and the competition. Understanding the regulatory environment allows the program team to select the endpoints most likely to be accepted by regulators for product approval. A strong understanding of the competitive environment allows the opportunity for a program design with elements superior to current and future competitive products, optimizing the new product’s market value. Examples of data that can support a marketing advantage include the study of more inclusive patient populations and the inclusion of clinically important secondary endpoints.³ These environments are dynamic and, therefore, need to be monitored on an ongoing basis, so the program can be adapted to respond to significant changes.

Initial phase 1-3 planning
Once desired labeling claims have been identified and the regulatory environment understood, phase 3 pivotal registration trials can be outlined to help the development team identify the evidence that will ultimately be necessary for the approval of those claims. Important elements for consideration include patient population inclusion and exclusion criteria, treatment
arms and comparators, and the primary and secondary endpoints to be measured.

Similarly, once phase 3 trials have been outlined, the phase 2 data needed to enable the conduct of phase 3 trials can be envisioned. This allows phase 2 trials to be designed to deliver the required information to make optimal phase 3 design decisions. Key phase 2 trial elements will be dose selection studies and will explore the breadth of endpoints being considered for the phase 3 trial. Pharmacokinetic and pharmacodynamic assessments can also be important contributors to future trial design.

In turn, defining the needs of phase 2 and 3 trial design can then influence phase 1 trial design and optimize the generation of information, which will help move the product quickly into phase 2. It should be noted that these insights will be combined with learnings from the preclinical program to finalize phase 1 design. Figure 1 is an illustration of this reverse engineering process.

**Tools for planning clinical development**

Working backward, based on a conceptualized final product, a first step would be to examine competitors’ product labeling statements. One of the most comprehensive databases for US labeling is DailyMed, a site sponsored by the National Institutes of Health and the National Library of Medicine.4 This site can be searched by trade or generic name, and the advanced search feature allows searches of various label sections. For example, indications sections can be searched to identify medications approved for specific diseases. For EU labeling, the Electronic Medicines Compendium has similar capabilities.5 Clinical trial endpoint choices evolve constantly, and there is no comprehensive database. Accordingly, the best option is to examine currently used endpoints in the therapeutic area of interest.

An important approach to identify clinical trial endpoints is searching the ClinicalTrials.gov website.6 This website was established to increase clinical trial transparency and lists each trial’s primary and secondary endpoints, thus allowing identification of currently used endpoints. The advanced search feature allows queries by disease or condition, as well as by development phase or outcome measure. The website can also provide important intelligence on competitors’ products currently in development. The EU has a similar registry.7

In addition, there are databases for identifying specialized clinical trial endpoints. The Medical Outcomes Trust is a nonprofit organization that keeps a list of commonly used quality-of-life instruments.8 Optum (formerly QualityMetric) is a commercial endeavor offering research services related to the use of such instruments in medical research, and it also lists some available instruments.9 In 2012, oncology study clinical trial endpoints were summarized in an article by Slabiak.10 There also is a web-based cardiovascular outcome inventory.11

Another very important tool for clinical development planning is to examine regulatory precedents for other
products within the same therapeutic area. The US Food and Drug Administration (FDA) maintains Drugs@FDA, a database of approval documents. Many of the agency’s medical reviews that resulted in approval of a new medicine can be found here. These medical reviews (and often the statistical reviews) can provide great insight into choosing appropriate endpoints for trials. Useful information also can be found in the administrative and correspondence sections of the drug review documents, since there often are meeting minutes or other correspondence related to trial design selection. Similar information is available from the EU in the scientific discussion documents released for new product approvals. Other countries posting such information include Canada, Japan, and Australia.

Once information has been collected about possible endpoints, it can be summarized in a target product label. It is helpful to include an outline of proposed clinical trials in early development program drafts. Useful information might include a proposed title, patient population, number of participants, inclusion and exclusion criteria, primary and secondary objectives and endpoints, study design with treatment arms, key elements of study execution and elements of statistical analysis. The accompanying Table provides an example of a template that might be used for a clinical trial outline.

Estimated timelines are critical, and at this stage, it is appropriate to have an overall timeline showing the expected start and completion dates for key trials, along with proposed agency meetings and other milestones. An example of such a chart is shown in Figure 2.

**Importance of strategic planning**

Effective strategic planning is important for avoiding a prolonged clinical development program. Once desired labeling language has been selected, and endpoints and trial designs have been researched, an overall program design can be drafted. The overall design should try to balance speed with quality and creativity. Speed to market can be an important component of being competitive in today’s pharmaceutical market, so options for the fastest timeline to gain product approvals should be explored. The development program’s length is another important total development cost determinant. Creativity in designing endpoints and outcomes to highlight the new product’s advantages compared with those of current and near-term competitive products can be equally significant.

Ensuring early stage trials are conducted with a clear product vision is critical for avoiding a prolonged development program. Such programs can proceed for many years until a potential path to market is identified or, worse, investors lose confidence in the program.

Regulatory authorities increasingly recognize the challenges associated with drug development for certain indi-
cations and in special populations and have collaborated in the development of innovative development strategies. For example, the FDA has issued guidance documents for developing novel antimicrobials to treat resistant organisms\(^\text{17}\) and for drugs targeting rare diseases.\(^\text{18,19}\)

**Clinical trial design considerations**
A comprehensive review of clinical trial design and drug development phase 1, 2, and 3 specifics is beyond the scope of this article. The discussion below focuses on contemporary clinical program design elements of particular interest to the regulatory professional.

**Phase 1**
Phase 1 includes first-in-human studies and other small trials designed for initial new drug safety and tolerability testing. A robust phase 1 program can provide important data, not only to meet regulatory requirements, but also to inform phase 2 and phase 3 study designs (Table).

Adequate investment to ensure complete and optimized data sets generated during phase 1 may be quite cost effective, because trial size, duration, and costs increase as the product progresses from phase 1 through phase 3. Many drug-specific programmatic considerations will be predicated on data from the preclinical program. Efforts should be made to bridge the preclinical and clinical programs explicitly, including exposure-response relationships for both toxicity and biomarker responses. This bridging will provide confidence in the preclinical results’ predictive value. In addition, biomarker responses can provide proof-of-concept supporting the program and aid in dose selection for phase 2 studies, which can decrease the size and cost of those trials. Expanding the

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**Figure 2. Sample timeline with one option for displaying high-level information on program timing**

![Timeline](timeline.png)

<table>
<thead>
<tr>
<th>ID</th>
<th>Phase, task name</th>
<th>Duration</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phase 1 Single rising dose (Europe)</td>
<td>12 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pre-IND meeting</td>
<td>0 day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>File IND</td>
<td>0 day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Phase 1 14-day multidose normals/diabetics (MD#1)</td>
<td>12.6 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Phase 1 Bioequivalence study</td>
<td>11 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Phase 2 12-week BID D/R in diabetic neuropathy</td>
<td>45.6 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Phase 2 12-week BID D/R in postherpetic neuralgia</td>
<td>45.6 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Phase 2 6-week dose frequency</td>
<td>40 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Phase 2 6-week dose frequency</td>
<td>2 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>End of phase 2 Meetings in Europe (EMA)</td>
<td>2 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Phase 3 6-month diabetic neuropathy in US</td>
<td>72.6 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Phase 3 6-month diabetic neuropathy in Europe</td>
<td>72.6 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Phase 3 6-month postherpetic neuralgia in US</td>
<td>72.6 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Phase 3 6-month postherpetic neuralgia in Europe</td>
<td>72.6 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>MAA/NDA preparation</td>
<td>93 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**
BID, twice daily; D/R, dose response; EMA, European Medicines Agency; FDA, [US] Food and Drug Administration; IND, investigational new drug; MAA, marketing authorization application; NDA, new drug application.
phase 1 population's diversity in terms of race, age, and sex will enhance the predictive value of data obtained.

Of note, pharmacokinetic data obtained in initial phase 1 studies are necessary but may be insufficient to complete a regulatory submission. Pharmacokinetic data obtained in the target population during phase 2 and phase 3 may be critical to understanding variability in exposure as well as exposure-efficacy and exposure-toxicity relationships. Additional pharmacokinetic studies in special populations, including patients with renal disease or liver disease, may be required but usually can be done in parallel with later-phase clinical studies to avoid programmatic delays.

Pharmacokinetic data in pediatric age groups also may be needed, depending on the drug's indication. Pediatric pharmacokinetics also are useful in bridging efficacy data obtained in adult populations to pediatric patients.20

Phase 2

Phase 2 objectives are to define the new drug's optimal dose(s), provide additional safety data, and confirm the drug's hypothetical efficacy. Often, the importance of proper dose selection is under-appreciated. A full understanding of dose selection not only is required for proper phase 3 design but is an integral part of regulatory evaluation. Research has found that 15.9% of failed first-time applications for new molecular entities were due to uncertainties related to dose selection.21 The complete data sets (preclinical and all clinical studies) ultimately will inform the optimal dose assessment. Nonetheless, phase 2 trials should include enough randomized dose experience to support evidence-based dose selection. Rigorous assessments of tolerability, adverse events, and efficacy all are required for the integrated benefit-risk assessment across doses.

The phase 2 program also should yield estimates of the drug's effect on the primary endpoint of interest to allow phase 3 study designs. Implicit in this objective is defining the primary endpoint to support the clinical indication. With few exceptions (see Phase 3 section), phase 3 primary endpoints must be unambiguous in clinical meaning and importance. In some cases, phase 3 endpoint choice may be clear (e.g., all-cause mortality), but the phase 2 program may be too small to detect drug effects on the clinical endpoint. In this case, phase 2 studies may incorporate surrogate or biomarker endpoints whose relationship to the clinical endpoint is well established and quantitatively predictable. In the absence of such biomarkers, drug efficacy uncertainty may persist until phase 3 completion. For example, this is currently true for therapeutics targeting critical limb ischemia due to peripheral arterial disease and has resulted in several failed phase 3 programs. Thus, investing early in defining useful biomarkers may be important in decreasing investment risk for such programs.

Clinical endpoint selection for indications not based on survival may be very challenging. The use of a biomarker associated with clinical status and modifiable by the drug is very attractive from a developmental perspective. However, the limitations of surrogate or biomarker endpoints are well understood, and there are many examples in which a drug was effective in changing the biomarker, as intended, but was not associated with the anticipated clinical effect.22 In the US, blood pressure, hemoglobin A1C, and LDL-cholesterol are among the few generally accepted surrogate endpoints for full drug approval. In other conditions, the sponsor must define a measure of clinical benefit that can meet regulatory standards. Phase 2 provides an opportunity to assess several endpoints, gain a better understanding of their clinical importance, and inform phase 3 endpoint selection. This process may require additional research. For example, it may be necessary to develop a validated patient-reported outcome tool or define the minimal clinically important change for the target population using a specific assessment modality.

Innovative approaches may be required and, if based on sound clinical and scientific work, can support successful regulatory submissions (Case Study 1).

Robust safety assessments also are part of the phase 2 program. Phase 2 should carefully assess adverse events of special interest based on the drug's mechanism of
action, preclinical signals, target patient population and prior experience with drugs in the same class. While the phase 2 program likely will be too small to allow definitive quantitative assessment of these events, focusing on them will be useful in defining optimal dose selection and establishing any special assessment methodologies required in phase 3. For example, more frequent assessment of safety biomarkers or establishing an event adjudication committee may be required.

Thus, as was the case with phase 1, approaching phase 2 trial design as an integral component of the total development program will ensure optimal data are generated to support both phase 3 design and the final submission.

**Phase 3**

Phase 3 trials provide definitive data on a new drug’s efficacy and safety. These data must meet explicit regulatory standards. Thus, in addition to a high degree of study integrity, the data must address the need for evidence to satisfy statistical, clinical and other scientific standards. As previously discussed in this article, many design criteria for phase 3 trials, including endpoint selection, are defined in phase 2. In general, phase 3 trials will be randomized, parallel-group, double-blind, comparator-controlled trials. Although alternative designs may be necessary based on the drug or target population, they will have to be justified rigorously, and steps should be taken to mitigate any biases that may be introduced through design compromises. The interpretability of study results is facilitated by using a placebo comparator.²³,²⁴ If an active comparator is chosen, then its efficacy and safety must be well established to allow meaningful inferences from the trial results. This is particularly important if a noninferiority hypothesis is tested, as opposed to a superiority hypothesis.²⁵

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**Case study 1. Selection of a clinically meaningful endpoint**

**Teduglutide (Gattex)** a and the selection of a clinically meaningful endpoint

Patients with short bowel syndrome (SBS) may require total parenteral nutrition (TPN) to ensure adequate nutrition and fluid delivery to address intestinal malabsorption. The TPN requirement is recognized as having a substantially adverse impact on patient quality of life and is associated with complications related to vascular access. Teduglutide is an analog of a glucagon-like peptide and has proliferative effects on intestinal mucosa, resulting in enhanced absorption.² Based on this, teduglutide was developed to improve SBS patients’ fluid and nutrient absorption. Teduglutide’s ability to induce intestinal mucosa proliferation could be demonstrated in patients with SBS, but the question remained on how the clinical importance of these histologic and physiologic changes could be demonstrated. Teduglutide’s sponsor sought input from patients and SBS experts. This work suggested a 20% reduction in parenteral nutrition and intravenous fluid volume would be important to SBS patients requiring TPN. These findings were discussed with FDA, and a primary endpoint was developed using a responder definition of at least a 20% reduction in parenteral nutrition and intravenous fluid volume. Secondary endpoints were selected to support clinical interpretation of the primary endpoint and treatment effects. Using these endpoints, the trials were completed successfully, and the drug was approved in the US and EU. This program illustrates the need for careful consideration and the value of collaborative discussion to establish clinical meaningfulness of the phase 3 study endpoint.

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In a review of unsuccessful initial new drug approval applications in the US, Sacks and colleagues found that 13% of failures were owing to study endpoints of unclear clinical relevance, and another 13% to inconsistent results when different endpoints were selected. These results illustrate the importance of proper primary and secondary endpoint selection. Primary endpoints must be of established clinical importance, and secondary endpoints must support both the drug’s efficacy and its clinical relevance. Failure to use the phase 2 program to define endpoints and estimate effect sizes to justify phase 3 endpoints and sample sizes will increase the risks of programmatic failure. In the US, submission of a special protocol assessment (SPA) can ensure alignment between the sponsor and FDA on critical trial design considerations. The SPA process may be especially useful if a nontraditional trial design is proposed or a more innovative methodology, such as an adaptive design, is used.

In the US, there are two important exceptions to the need for definitive clinical endpoint data before approval.

- **Accelerated approval.** This allows marketing approval based on a surrogate endpoint when there is an important, unmet clinical need and high likelihood the surrogate endpoint is predictive of clinical benefit.
Case study 3. Excluding unacceptable risk

Antidiabetes drugs and possible cardiovascular risk

It is challenging to establish the safety of an antidiabetes drug against a high background clinical event rate due to the natural history of diabetes. Under these conditions adverse events observed during development cannot easily be differentiated as drug-induced vs natural history. A similar challenge likely contributed to delayed recognition of the association between cyclooxygenase inhibitors use and myocardial infarctions. A 2007 meta-analysis suggested rosiglitazone (Avandia)\(^a\) might be associated with an increase in cardiovascular events in patients with type 2 diabetes.\(^b\) Although the analysis suggested the increased event rate would be clinically important, individual phase 3 clinical trials would have been too small to accrue sufficient adverse events to allow detection of the hypothesized risk. Since multiple drug classes were available to treat type 2 diabetes, the FDA felt any new antidiabetes treatments should have little residual uncertainty with respect to their cardiovascular risk.

The agency issued guidance requiring new antidiabetes drugs to demonstrate they were not associated with unacceptable cardiovascular risk.\(^c\) This guidance suggests sponsors provide data excluding a relative risk of 1.3 for cardiovascular events for any new antidiabetes drug. This requirement can be met postapproval if preapproval data exclude a relative risk of 1.8. As a result, phase 3 trials for drugs to treat type 2 diabetes include special procedures for identifying and adjudicating potential cardiovascular events. Accruing sufficient adverse events to exclude a relative risk of 1.3 requires studying higher-risk patients and/or large sample sizes. For example, the postmarketing study examining saxagliptin (Onglyza)\(^d\) and cardiovascular outcomes randomized 16,492 patients and followed them for a median of 2.1 years.\(^e\) Of note, the original signal suggesting a potential cardiovascular risk associated with rosiglitazone may have been false positive.\(^f\)

In March 2020, the FDA withdrew the 2008 guidance and replaced it with an updated guidance for industry, titled Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control.\(^g\)

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conduct studies to demonstrate the drug’s actual clinical benefit.

- **Use of animal models.** The second exception is based on the Animal Rule. The rule can be used to obtain marketing approval based on demonstrating efficacy in animal models that are likely to be predictive of response to the disease when combined with human drug safety data. It can be used only when human clinical trials would be unethical or impractical. The Animal Rule was enacted to permit drug development for conditions, such as radiation poisoning or infectious diseases, with high lethality that might be used in terrorist attacks or encountered naturally (e.g., the Ebola virus).

Phase 3 trial size is increasingly being determined by the need to meet safety requirements rather than the number of patients required to demonstrate efficacy. Demonstrating safety can no longer be viewed as failure to observe adverse effects. Rather, sponsors must demonstrate that trial procedures were adequate to recognize and define adverse events, especially those designated as events of special interest (Case Study 2). Further, the clinical trial must be large enough to ensure unacceptable adverse events have been excluded using statistically appropriate methods. Formal procedures are important, particularly if a drug has the potential to increase the rate of serious adverse events that occur at a background rate in the target population (Case Study 3).

Thus, phase 3 data must be sufficient, quantitatively and qualitatively, to provide definitive evidence of both safety and efficacy. The totality of the data, including preclinical studies and all clinical trials, form the basis for regulatory decision making and the information ultimately included in the approved product’s labeling.

**Conclusion**

Developing an optimal strategy clinical development for a new product is difficult. It requires research and critical thinking. Nonetheless, the opportunities exist for the outcome to be a product with more effective marketing claims and with a supporting set of data which meets the needs of regulators.

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**About the authors**

**William Sietsema, PhD,** is vice president, global regulatory affairs at Caladrius Biosciences. Previously, Sietsema was global regulatory lead at Amgen, vice president, global regulatory consulting and submissions at Kendle International/INC Research, and adjunct professor of pharmaceutical sciences at the University of Cincinnati, College of Pharmacy. He received his doctorate degree in biochemistry from the University of Wisconsin, Madison. He is the author of 40 journal articles, six book chapters, 73 presentations and posters, and is an inventor on six patents. He has published eight books on various regulatory topics. He is a member of the American Chemical Society, the Association for Regenerative Medicine, and the Regulatory Affairs Professionals Society, where he currently serves on the Editorial Advisory Committee. He can be contacted at william@sietsema.com.

**Eric Brass, MD, PhD,** is professor emeritus of medicine at UCLA School of Medicine. Brass has longstanding research interests in drug discovery, development, and regulatory issues, and is a frequent lecturer and consultant in these areas. He has worked on development programs in a number of therapeutic areas, including those related to cardiovascular, diabetes, and other metabolic diseases. Brass has authored over 200 scientific papers, review articles, and book chapters. He can be contacted at ebrass@ucla.edu.

**Acknowledgment**

This article is based on a chapter in the second edition of *Global Pharmaceutical and Biologics Regulatory Strategy* (Sietsema WK, Brass E. Strategies for clinical development planning. In: Sietsema WK, Meacham MM, eds. Global pharmaceutical and biologics regulatory strategy. 2nd ed. Rockville, MD: Regulatory Affairs Professionals Society; 2020:89-98).

**Citation**


**References**


Clinical trials, good clinical practice, regulations, and compliance

This article provides an overview of the international and national guidelines associated with clinical trials. The authors highlight the importance of multiregional clinical trials and outline the principles of good clinical practice (GCP) and regulatory compliance.

Introduction
Clinical trials are essential components of pharmaceutical research and development. A clinical development program’s broad aim is to treat a specific indication in a certain population to test whether a drug is simultaneously safe and effective and whether its benefit-risk relationship is acceptable.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. A clinical trial requires that the GCP standard compliance 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 World Medical Association’s Declaration of Helsinki, and that the clinical trial data are credible. The objective of the International Council on Harmonisation (ICH) GCP Guideline is to provide a unified standard for a mutual acceptance of human clinical data by the European Union (EU), US, and Japanese regulatory authorities and their jurisdictions. The GCP is a global norm required to be applied for the conduct of human clinical trials globally.

Clinical trials serve to establish safety and efficacy and develop new treatment regimens of new medicines. Clinical trials results establish essential data for the regulatory approval of new medicines and therapeutic treatments by global regulatory authorities.

Multiregional clinical trials
Rise of the MRCT
Historically, drug development focused on regulatory strategies designed for specific national geographies and regulatory jurisdictions. However, this compartmentalized approach led to the ethical issues because clinical trials were duplicated to support a single region’s requirements. Subsequently, increased international commerce and pharmaceutical industry mergers have globalized the drug development approach, resulting in multiregional clinical trials (MRCTs), which have become more common. An MRCT is a clinical trial conducted simultaneously in multiple countries under a single protocol, with the objective of providing consolidated clinical data to support marketing authorization application submissions across multiple regions.

Conducting an MRCT can be a useful development strategy, but it can present operational and scientific challenges,
because clinical trials are governed and supervised at the national level, and there is no completely harmonized regulatory approach for their conduct. Regulators such as the European Medicines Agency, US Food and Drug Administration, Japanese Pharmaceuticals and Medical Devices Agency, and China’s National Medical Products Administration have released country-specific guidance for sponsors on using foreign data (that is, extrapolating results from studies conducted outside the region to the local population) to support marketing authorization applications. However, although this is encouraging for development companies, there remains a lack of harmonization. To address this issue, the ICH has released draft guidance (ICH E17) that can be used as a basis for unapproved drugs in clinical development, even though it was written primarily to address postmarket trials.

**MRCTs’ value in drug development**

Global regulatory strategies are used to facilitate simultaneous global drug development, allowing companies to plan and conduct trials more efficiently to facilitate more rapid product availability to patients worldwide. Proper MRCT planning and conduct are critical to this effort. MRCTs allow an examination of a treatment’s applicability to a diverse population. Intrinsic and extrinsic factors believed and/or suspected of affecting drug responses can be further evaluated based on data from multiple ethnicities in various regions, using a single protocol. This strategy reduces the number of separate clinical trials conducted in each region, thereby avoiding the ethical issue of unnecessary duplication of studies.

**MRCT planning issues**

MRCTs pose their own unique set of regulatory and ethical issues. There are a number of key considerations for conducting MRCTs, which can be broken into five basic categories: statistical, clinical, essential documents, operational, and regulatory.

**Statistical.** For any clinical trial, but especially for an MRCT, it is important to have a robust statistical analysis plan from the outset. Sample size calculations and statistically relevant justifications are critical, to ensure that the predicted outcome reflects considered for the entire population across regions and remains consistent to support country-specific population predictions.

No specific method has been established to calculate sample size, but the guiding principle for determining the overall MRCT sample size is that the primary hypothesis test can be assessed, based on combining data from all trial regions (i.e., primary endpoints should be acceptable to all individual regions). Subgroups defined according to common intrinsic and/or extrinsic factors (e.g., disease stage, race, ethnicity, genetic factors, etc.) can be useful to generate key scientific evidence to support regional or national marketing authorizations.

In accordance with ICH integrated addendum E6(R2), the following are applicable:

- A description of the statistical methods to be used, including timing of any planned interim analysis(s).
- The number of subjects planned to be enrolled. In multicenter trials, the projected numbers of enrolled subjects for each trial site should be specified. The reason for sample size choice, including reflections on (or calculations of) the power of the trial and clinical justification.
- The level of significance to be used.
- Criteria for trial termination.
• Procedure for accounting for missing, unused, and spurious data.
• Procedures for reporting any deviation(s) from the original statistical plan (any deviation[s] from the original statistical plan should be described and justified in the protocol and/or the final report, as appropriate).
• The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

Clinical. Clinical factors – such as disease incidence, prevalence, differences in standard of care, baseline demographics (such as height, body weight, etc.) – can vary across regions and should be taken into account and minimized when designing the protocol. Minor differences in medical practice (e.g., disease definitions, adverse event reporting, etc.) across regions generally are acceptable. Study personnel training should be planned before initiating the trial to reduce the impact of any differences.

Essential documents for conducting clinical trials. Essential documents are those that individually and collectively permit trial conduct and data quality to be evaluated. These documents demonstrate the investigator, sponsor, and monitor’s compliance with GCP standards and all applicable regulatory requirements.

Essential documents serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in successful investigator, sponsor, and monitor trial management. These documents also are the ones most often audited by the sponsor’s independent audit function and inspected by the regulatory authority(ies) in the process to confirm the trial conduct validity and data integrity.

A list of minimum essential documents to be developed follows. These various essential documents are grouped into three sections, based on the clinical trial stage during which they are normally generated:
1. Before the trial’s clinical phase commences.
2. During the trial’s clinical conduct.
3. After the trial’s completion or termination.

The ICH E6(R2) describes each document’s purpose and whether it should be filed by the investigator/institution or sponsor, or by both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files (TMFs) should be established at the beginning of the trial, both at the investigator/institution’s site and the sponsor’s office. A final trial close-out can be done only after the monitor has reviewed both investigator/institution and sponsor files and confirmed all necessary documents are in the appropriate files.

Any or all of the documents addressed in ICH E6(R2) may be subject to, and should be available for, audit by the sponsor’s auditor and inspection by the regulatory authority(ies).

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents, including the source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval. The sponsor should ensure the investigator has control of and continuous access to the case report form (CRF) data reported to the sponsor. The sponsor should not have exclusive control of those data.

In accordance with the ICH E6(R2), the institutional review board (IRB) or independent ethics committee (IEC) should retain all relevant records for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies). (Relevant records would include written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence.) 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. 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).4

Operational. Operational issues, such as protocol compliance variability across regions and sites (e.g., differences in follow-up, compliance with study medication, etc.), should be identified and mitigated in advance, wherever possible. Medicine supply is a complex MRCT issue requiring intricate advance planning, and issues such as comparator choice give rise to a number of questions (e.g., What international treatment guidelines apply? Is access to standard therapies comparable across regions? Is the placebo an acceptable comparator? Are good manufacturing practices (GMP) regulations comparable and under which conditions a study medication manufactured in one country can be distributed to the other countries? etc.).

Labeling is also an MRCT issue because each country has its own local jurisdiction-based labeling requirements. Once the clinical trial has been approved, medicine supply issues require constant vigilance, adaptation, and considerable organizational capacity and resources. (Supply issues would include dealing with shelf-life extensions; temperature-controlled distribution; country-specific storage [warehouse, supply chain]; national customs requirements and import and export licenses for biological samples, etc.)

Regulatory. Regulatory and ethical issues include understanding and adhering to the relevant country and local statutes regarding regulatory authority, ethics committee reviews, informed consent document requirements, GMP requirements, trial data privacy requirements, and so on. It is critical that the sponsor understands the relevant local regulatory legislation, because once clinical trials have been initiated simultaneously in multiple clinical sites or countries, the trial must adhere to the ICH’s good clinical practice norm and compliance requirements.

ICH GCP
ICH intro
In April 1990, regulatory agencies from the EU, US, and Japan and pharmaceutical industry experts from those three Tier 1 regions met at the first International Conference for Harmonisation to discuss how to ensure safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner while protecting public health. The committee focused harmonization efforts on the three main criteria that are the basis for approving and authorizing new medicinal products globally: safety, efficacy, and quality.

ICH has played an important role, developing more than 60 international guidelines for pharmaceutical development and registration. In 2015, it celebrated 25 years of successful harmonization by announcing its intention to expand its membership. It included the regulatory agencies from Canada and Switzerland as standing regulatory members, added other agencies and organizations as observers, and changed its name to International Council for Harmonisation, to establish itself as a truly global platform for pharmaceutical regulatory harmonization.5

As of May 2020, in addition to the full regulatory members listed above, the ICH association also counts the following regulatory authorities among its full regulatory members:6

It is critical that the sponsor understands the relevant local regulatory legislation, because once clinical trials have been initiated simultaneously in multiple clinical sites or countries, the trial must adhere to the ICH’s good clinical practice norm and compliance requirements.
Besides these full regulatory members, the ICH E6(R2) includes other regulatory authorities, member organizations, and industry members and invites an increasing numbers of organizations as so-called observers. ICH observers actively contribute to the organization’s work. They are nonvoting ICH steering committee members and can designate experts to participate in all technical discussions or submit new ICH topic proposals to the committee. ICH guidelines are approved by ICH members and adopted by national regulatory authorities.7

In April 1996, ICH released one of the most important guidance documents in clinical research: its good clinical practice guideline (GCP E6).4 Its objective was to provide a unified standard for the EU, US, and Japan to facilitate mutual acceptance of clinical data by all three jurisdictions’ regulatory authorities. As the ICH’s reach has expanded, and drug development has become more globalized, its GCP guidance has become the gold standard for clinical trials. The ICH-GCP guideline E6 has undergone two revisions since its inception. The most current version, the integrated addendum ICH-GCP E6 Revision 2 (R2), dates from November 2016 and has since been implemented into many national laws. In June 2019, ICH started working on a next complete update version of the GCP guideline as part of its continuing efforts to keep track of the ever-changing and evolving clinical trial arena.

GCP – E6

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

The overall objective of the ICH GCP guideline (E6[R2]) is to provide a unified standard for the EU, US, and Japan (and the other ICH regions) to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guideline was developed with consideration of current GCPs in those regions, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO). This guideline should be followed when generating clinical trial data intended to be submitted to regulatory authorities.

ICH E6(R2)’s principles also may be applied to other clinical investigations that may have an impact on human subjects’ safety and well-being.

GCP’s foundations began in 1947, when Nazi war criminals were tried for their crimes in Nuremberg at the end of World War 2. Among those tried were Nazi doctors who had performed human trials without the consent of the subjects, many of whom died as a result of the experiments. At the end of the trial, the 10-point Nuremberg Code8 was released. Its general principles focused on protecting consenting research subjects by avoiding unnecessary suffering, prioritizing subjects’ rights (including the right to withdraw from the trial), and conducting trials in accordance with sound scientific principles. These general principles still form the general basis of the guideline that governs the ethical conduct of human research today.

Also in 1947, the World Medical Association was formed to establish and promote the highest possible standards of ethical behavior and care by physicians. In 1964, the association published a set of ethical principles for physicians performing research in humans, the Declaration of Helsinki.1 This declaration developed the Nuremberg Code’s existing principles, notably adding
the requirement for IEC review of research. It has been reviewed and revised frequently to remain relevant, with the most recent version released in 2013. Adherence to the Declaration of Helsinki is not just a legal, but a moral requirement, and it is frequently cited by ethics committees and forms the first ICH GCP principle.

**ICH GCP (E6[R2]) principles.** The key principles for good clinical practice are:

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. 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.
3. The rights, safety, and well-being of trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior IRB/IEC approval/favorable opinion.
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.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject before clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. (Addendum E6[R2].) This principle applies to all records referenced in this guideline, regardless of the type of media used.)
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).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable GMP. They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented. (Addendum E6[R2]. Aspects of the trial essential to ensure human subject protection and reliability of trial results should be the focus of such systems.)

**Regulations**

**ICH guidance**

ICH has a number of other useful guidance documents, summarized below, that should be considered when planning clinical trials.

**E2: Safety reporting.** Methods of collecting and handling safety and efficacy information should be standardized across participating countries. Safety reporting should be conducted in accordance with ICH E2A-E2F (pharmacovigilance). Where local regulations specify different requirements (e.g., expedited reporting timelines), local adherence is required. Investigators should be trained appropriately on safety reporting requirements.

**E5(R1): Ethnic factors in the acceptability of foreign clinical data.** In 1998, ICH implemented its E5 guideline, allowing a supplemental clinical trial known as a “bridging study.” Bridging studies are intended to provide pharmacodynamic, pharmacokinetic, or clinical data to enable extrapolation of foreign clinical data to “new” regions. In other words, clinical trial data from Western countries could be extrapolated to other regions (or vice versa) and used for submission purposes, depending on bridging study results (Figure 1).

**E8: General considerations for clinical trials.** ICH E8 describes internationally accepted principles and practices for conducting both individual new medicinal product clinical trials and overall development strategy.
It covers issues and considerations relating to the development plan and to its individual component studies and describes a number of special circumstances and populations requiring specific consideration when part of such a development plan (e.g., drug metabolite studies, drug-drug interactions, special populations, etc.). The guideline also covers key principles in planning a clinical trial's objectives, design, conduct, analysis, and reporting.

ICH is currently working on an updated version “Revision 1/R1,” that is available as a draft guideline. There are three main areas that will be changed and/or added. The revised E8(R1) guideline will:

1. Identify a basic set of critical-to-quality factors that can be adapted to different types of trials to support the meaningfulness and reliability of trial results and to protect human subjects. Examples of these factors would include eligibility criteria, masking, types of controls, outcome ascertainment, site feasibility, safety monitoring, statistical analysis, and investigational product handling and administration.

2. Address a broader range of trial designs and data sources.

3. Provide an updated comprehensive guide to, or cross-referencing of, all other relevant ICH guidelines that inform the design, planning, and conduct of clinical research, without reproducing the detailed material found in those guidelines.

E9: Statistical principles for clinical trials. ICH E9 provides general principles for planning and conducting randomized clinical trials' statistical analyses. Each clinical trial contributing to a marketing application should specify all important details of its design and conduct, and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins. This guideline gives detail on tri-
al design (such as choice of endpoints, blinding, sample size, etc.), study conduct (such as monitoring, interim analysis and early termination), data analysis considerations, data evaluation, and results’ reporting.

The ICH E9(R1) is an addendum to the original ICH E9 that clarifies and extends ICH E9. For example, the original ICH E9 introduced the intention-to-treat (ITT) principle in regard to the effect of a treatment policy in a randomized controlled trial. Under the ITT principle, subjects are followed, assessed, and analyzed irrespective of their compliance to the planned course of treatment, indicating that preservation of randomization provides a secure foundation for statistical tests. The addendum establishes that the ITT principle requires that the trial analysis should include all subjects relevant for the research question, and that subjects should be included in the analysis as randomized.

The addendum also revisits the issues generally considered under data handling and “missing data; the issues around the concept of analysis sets in the framework, including the related recommendations; and the concept of robustness expanding under the heading of sensitivity analysis. A distinction is made between the sensitivity of inference to the assumptions of a chosen method of analysis and the sensitivity to the choice of analytic approach more broadly.

**E10: Choice of control group and related issues in clinical trials.** The control group choice is always a critical decision in clinical trial design. ICH E10 describes the control group’s purpose and control group types commonly used to demonstrate efficacy. It discusses critical design and interpretation issues associated with an active control trial’s use to demonstrate efficacy by showing noninferiority or equivalence to the

**Table 1. Regional regulatory authorities**

<table>
<thead>
<tr>
<th>Region</th>
<th>Regulatory authority</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Therapeutic Goods Administration (TGA)</td>
<td><a href="https://www.tga.gov.au/">https://www.tga.gov.au/</a></td>
</tr>
<tr>
<td>Chinese Taipei</td>
<td>Taiwan Food and Drug Administration (TFDA)</td>
<td><a href="https://www.fda.gov.tw/ENG">https://www.fda.gov.tw/ENG</a></td>
</tr>
<tr>
<td>Europe (national agency links)</td>
<td>Head of Medicines Agencies (HMA; medicines agency websites in EU)</td>
<td><a href="http://www.hma.eu/nationalcontacts_hum.html">http://www.hma.eu/nationalcontacts_hum.html</a></td>
</tr>
<tr>
<td>Japan</td>
<td>Pharmaceuticals and Medical Devices Agency (PMDA)</td>
<td><a href="http://www.pmda.go.jp/english/about-pmda/">http://www.pmda.go.jp/english/about-pmda/</a></td>
</tr>
<tr>
<td>Singapore</td>
<td>Health Sciences Authority (HSA)</td>
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</tr>
<tr>
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<td>South African Health Products Regulatory Authority (SAHPRA)</td>
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<tr>
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</tr>
<tr>
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<td>Turkish Medicines and Medical Devices Agency (TMMDA/TITCK)</td>
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</tr>
<tr>
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<td>Food and Drug Administration (FDA)</td>
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RegulatoryFocus.org March 2021
control. The guideline also has detailed considerations on a number of different control group types.

**Regional regulations**

Although ICH has been adopted as guidance in many regions, it is important to have a full and thorough understanding of the specific country’s regulatory landscape before commencing any clinical trial, because local regulatory requirements may differ from the guidance – for example, the US has stricter IRB regulation requirements than ICH’s GCP.

There are a number of sources for regulatory information, but there is no single place to find it all. A good starting point for this kind of information is to visit national regulatory or health authority websites (Table 1).

Other resources for agency information can be found on the Parenteral Drug Association and World Health Organization websites. Specifically, there will be a significant paradigm shift in the approval process for clinical trials within the EU’s 27 member states. At the end of 2021, it is anticipated that the EU Regulation 536/2014 will enter into application and replace the EU Directive 2001/20/EC. That means the essential documents of a clinical trial will be divided into 2 parts – Part 1, addressing general aspects of a trial, and Part 2, its national aspects. Part 1 will be reviewed only by a sponsor-selected, reporting EU member state, whereas Part 2 will be reviewed by all participating concerned member states. Review timelines will be shorter than current timelines, according to EU Directive 2001/20/EC.

**Compliance**

Compliance with GCP principles, including adequate human subject protection, is recognized universally as a critical requirement for conducting research involving human subjects. For studies conducted in the ICH regions, compliance with ICH E6(R2) provisions ensures studies will be accepted for review by ICH countries when marketing authorization applications are submitted.

Regulatory authorities and ethics committees use inspections and audits to monitor trial sponsor, institution, and investigator compliance with the protocol; standard operating procedures (SOPs); adherence to GCP E6(R2); and local regulatory requirements. Inspectors have the right to review quality management systems (QMS) to manage the trial and review trial master file documentation and source documents. The inspector may suspend a trial or place a trial site on hold, terminate a trial, or fine or imprison a person if any noncompliance issues are found.

**ICH E6(R2) – Specific definitions/terms**

**Adverse drug reaction (ADR).** In the preapproval clinical phase with a new product or new usage, all noxious and unintended responses to a medicinal product related to any dose should be considered and ADR, particularly because the therapeutic dose(s) may not be established. “Responses to a medicinal product” means a causal relationship between the product and an adverse event is, at least, a reasonable possibility, that is, the relationship cannot be ruled out.

For marketed medicinal products, an ADR is a response to a drug that is noxious and unintended and which occurs at doses normally used in humans for disease prophylaxis, diagnosis, therapy, or to modify physiological function.

**Adverse event (AE).** This is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product.

**Serious adverse event (SAE) or serious adverse drug reaction (serious ADR).** An SAE is 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 or birth defect.

**Audit trail.** This is documentation that allows reconstruction of the course of events.

**Blinding/masking.** Blinding or masking is 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).

**Case report form.** A CRF is 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.

**Clinical trial/study.** This is any investigation in human subjects intended to discover or verify an investigational product’s clinical, pharmacological, and/or other pharmacodynamic effects, and/or to identify any investigational product’s adverse reactions, and/or to study an investigational product’s absorption, distribution, metabolism, and excretion to ascertain its safety and/or efficacy. The terms “clinical trial” and “clinical study” are synonymous.

**Clinical trial/study report.** This report comprises a written description of a trial or 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.  

**Comparator (product).** This is an investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

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

**Contract research organization.** A CRO is an organization (commercial, academic, or other), or a person, contracted by the sponsor to perform one or more of a sponsor’s trial-related duties and functions. A sponsor may transfer any or all of its trial-related duties and functions to a CRO, but the ultimate responsibility for the trial data’s quality and integrity always resides with the sponsor. The CRO should implement quality assurance and quality control. Any trial-related duty and function transferred to and assumed by a CRO should be specified in writing.

**Efficacy assessment.** This assessment includes:
• Efficacy parameter specifications, and
• Methods and timing for assessing, recording and analyzing efficacy parameters.

**Independent data-monitoring committee.** The IDMC is also referred to as the data and safety monitoring board, monitoring committee, or data monitoring committee. The sponsor may establish an independent data-monitoring committee to periodically assess a clinical trial’s progress, safety data, and critical efficacy endpoints, and to recommend whether the sponsor should continue, modify, or stop a trial.

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

**Inspection.** A regulatory authority’s official review of documents, facilities, records, and any other resources the authority deems to be related to the clinical trial and that may be located at the site of the trial, at the sponsor and/or CRO’s facilities or at other establishments the regulatory authority deems appropriate.

**Institution (medical).** This is any public or private entity or agency or medical or dental facility where clinical trials are conducted.
Institutional review board. An IRB is an independent body constituted of medical, scientific, and non-scientific members, responsible for ensuring the rights, safety, and well-being of human subjects involved in a trial are protected by, among other things, reviewing, approving, and continually reviewing the trial protocol and amendments and the methods and material to be used in obtaining and documenting trial subjects’ informed consent.

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 to gain further information about an approved use.

Protocol. The protocol is an essential document that describes the trial’s objective(s), design, methodology, statistical considerations and organization. It usually also provides the trial’s background and rationale, but these could be provided in other protocol referenced documents. In the ICH GCP guideline, the term “protocol” refers to the protocol and protocol amendments.

Protocol amendment. An amendment is a written description of a change(s) to or formal clarification of a protocol.

Quality assurance. Quality assurance comprises all those planned and systematic actions established to ensure the trial is conducted properly and data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

Quality control. Quality control includes the operational techniques and activities undertaken within the quality assurance system to verify trial-related activities fulfil quality requirements.

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

Regulatory authorities. These bodies have the power to regulate. In the ICH GCP guideline, the term “regulatory authorities” includes authorities that review submitted clinical data and those that conduct inspections. These bodies sometimes are referred to as competent authorities.

Safety assessment. This includes:
  • Safety parameter specifications;
  • Methods and timing for assessing, recording, and analyzing safety parameters;
  • Procedures for eliciting reports of, and for, recording and reporting adverse events and intercurrent illnesses (those that intervene during the course or another disease); and
  • Type and duration of subject follow-up after adverse events.

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

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.

Standard operating procedures. SOPs are detailed, written instructions to achieve uniformity of the performance of a specific function.

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

Treatment of subjects. The treatment(s) to be administered (including all product names, the dose(s), dosing schedule(s), route or mode(s) of administration, and treatment period(s), including the follow-up period(s) for
subjects for each investigational product treatment, trial treatment group, or arm of the trial).

- Medication(s) and/or treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- Procedures for monitoring subject compliance.

**Quality management system**

Since the ICH GCP guideline's inception in 1996, the scale, complexity, and cost of clinical trials have increased, but little has changed in the guidance document. ICH addressed this, and, in November 2016, released the updated guidance to bring it into line with current clinical trial practices. It is aimed at encouraging the implementation of improved, more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting, while continuing to ensure human subject protection and data integrity.

The main change of the ICH E6(R2) is the introduction of Section 5.0, entitled Quality Management. This section emphasizes making sure that systems and procedures are in place throughout the trial to ensure compliance with ICH GCP. The quality management system should use a risk-based approach.

A QMS ensures a clinical trial is conducted to defined, uniform standards and that each regulatory process step is identified and documented. This commonly is referred to as the set of processes, or SOPs, and use of tools to which the trial must adhere. Strictly speaking, the QMS should also include SOP adherence reviews, for example, through quality checks or documentation audits (Figure 2).

**ICH E6(R2) – Specific requirements for sponsors**

**Sponsor’s quality management**

Sponsors should implement systems to manage quality throughout all trial process stages. They should focus on trial activities essential to ensuring human subject protection and trial result reliability. Quality management includes designing efficient clinical trial protocols and tools and procedures for data collection and processing, as well as collecting information essential to decision making.

The methods used to assure and control trial quality should be proportionate to the trial's inherent risks and the importance of the information collected. The sponsor should ensure all trial aspects are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, case report forms and other operational documents should be clear, concise and consistent.

The quality management system should use a risk-based approach as described below. If CROs are contracted, the CROs should also implement quality assurance and quality control.

- **Critical process and data identification.** During protocol development, the sponsor should identify those processes and data critical to ensuring human subject protection and trial result reliability.

- **Risk identification.** The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).
Risk evaluation. The sponsor should evaluate the identified risks against existing risk controls by considering the:
• Likelihood of errors occurring,
• Extent to which such errors would be detectable, and
• Impact of such errors on human subject protection and trial result reliability.

Risk control. The sponsor should decide which risks to reduce and/or accept. The approach used to reduce risk to an acceptable level should be proportionate to the risk’s significance. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the variables’ medical and statistical characteristics as well as the trial’s statistical design, to identify systematic issues that can affect subject safety or trial result reliability. Detecting deviations from the predefined quality tolerance limits should trigger an evaluation to determine whether action is needed.

Risk communication. The sponsor should document quality management activities. It should communicate quality management activities to those who are involved in or affected by them, to facilitate risk review and continual improvement during clinical trial execution.

Risk review. The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking emerging knowledge and experience into account.

Risk reporting. The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (see ICH E3, Section 9.6 on Data Quality Assurance).

Quality assurance and quality control
• The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure trials are conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).
• The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial-related sites, source data, and documents and reports for sponsor monitoring and auditing, as well as inspection by domestic and foreign regulatory authorities.
• Quality control should be applied to each data handling stage to ensure all data are reliable and have been processed correctly.
• Agreements the sponsor makes 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.

Investigational products
The sponsor is responsible for timely delivery of sufficient quantities of investigational product to the investigator/institution. Investigational products should be characterized and manufactured according to applicable GMP, stable for the period of use, coded and labelled compliant to local regulations and not distributed before sponsor obtains all required documentation. A system for blinding and unblinding, when applicable, rapid identification of products and retrieval of unused, expired or recalled products should be in place.

Contract research organization
• A sponsor may transfer any or all of its trial-related duties and functions to a CRO, but the sponsor retains ultimate responsibility for trial data quality and integrity. The CRO should implement quality assurance and quality control.
• Any trial-related duty and function transferred to and assumed by a CRO should be specified in writing.
ICH E6(R2) addendum. The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions subcontracted to another party by the sponsor’s contracted CRO(s).

- Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.
- All references to a sponsor in E6(R2) also apply to a CRO to the extent the CRO has assumed the sponsor’s trial-related duties and functions.

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

Compensation to subjects and investigators
If mandated by applicable regulatory requirement(s), the sponsor should provide insurance or indemnify (legal and financial coverage) the investigator or the institution against claims arising from the trial, except claims arising from malpractice and/or negligence.

Multicenter trials. For multicenter trials, the sponsor should ensure:
- All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favorable opinion by the IRB/IEC.
- CRFs are designed to capture the required data at all multicenter trial sites. For investigators who are collecting additional data, supplemental CRFs designed to capture the additional data also should be provided.
- The responsibilities of the coordinating investigator(s) and other participating investigators are documented prior to the trial’s start.
- All investigators are given instructions on following the protocol, complying with a uniform set of standards for assessing clinical and laboratory findings, and completing CRFs.
- Communication between investigators is facilitated.

Monitoring
The sponsor appoints appropriately trained, qualified monitors and ensures trials are adequately monitored. A systematic, prioritized, risk-based approach to monitoring clinical trials should be developed by the sponsor. The rationale to apply onsite monitoring versus central monitoring by remotely collected data should be documented in the monitoring plan.

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

Standard operating procedures
SOPs are detailed written instructions to achieve high level quality and uniformity in a specific clinical research function’s and systems performance. They define tasks, allocate responsibilities, detail processes, describe system validation and functionality testing, data collection and handling, indicate documents and templates to be used and cross-reference such other quality management tools as work instructions and guidance or policy documents. They are standards against which the clinical trial and computerized systems may be audited or inspected. SOPs are developed by experts in their fields and intended to encourage best practices. Where applicable, SOPs include instructions from regulations, standards, guidelines and any other applicable policies; users complying with these will adhere to the SOP.

Tools – Quality control documents
Quality control documents (QCDs) help control certain tasks’ quality. They typically are documents included in a QMS to help the user follow a particular set of SOP instructions. Examples are templates (e.g., submission cover letters), checklists (e.g., quality control checklists) and forms (e.g., label review checklists). Using QCDs may be optional or mandatory, as defined within their parent SOPs.
**Trial master file**

A TMF is a collection of the essential documents a sponsor uses to record how it has fulfilled its clinical trial obligations. The file should be established at the beginning of every trial. The ICH E8 defines essential documents as “documents which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated.” Essential documents demonstrate the investigator, sponsor, and site’s compliance with the protocol, GCP, and all applicable regulatory requirements. They can be inspected by regulatory authorities at any time during and after the study is completed and submitted for product approval. Essential documents must be maintained securely in a location also immediately accessible for study team use and inspectors. The minimum list of essential documents is defined in ICH E6(R2). Data can be organized into 11 broad categories (Table 2).

The sponsor should file relevant essential documents to the TMF, site, and third parties involved before, during, and after the clinical trial.

**Source documents**

Source documents are any original documents related to the trial, medical treatment and trial subject history before, during and after trial involvement. Source documentation should allow an auditor to reconstruct a trial’s events as they happened. One of the most common findings in investigator site inspections is lack of reliable, accurate and adequate source documentation. ICH E6(R2) discusses good documentation practices and introduces the notion of ALCOA-C⁴ (attributable, legible, contemporaneous, original, accurate, and complete documents). Sites should be trained on GDPs, and source documentation should be monitored regularly to ensure compliance.

**Conclusion**

Planning and conducting a clinical trial, whether in single or multiple regions, requires in-depth knowledge of international GCP, regional and national legislation, regulations, guidances and best practices. Compliance with ICH GCP is a key element to ensure that rights, safety, and well-being of the trial subjects is safeguarded and that clinical trial data are valid, credible and acceptable for drug registration purposes. It should be noted that each country has incorporated GCP principles into its national laws and regulations and may have stricter requirements than those of ICH. The regulatory landscape should be monitored continuously, and study conduct should be adapted to ensure it meets all national and international regulatory practices consistently.

**Abbreviations**

ADR, adverse drug reaction; AE, adverse event; CRF, case report form; CRO, contract research organization; GCP, good clinical practice; GMP, good manufacturing practices; MRCTs, multiregional clinical trials; IEC, independent ethics committee; IRB, institutional review board; ITT, intention-to-treat; ICH, International Council on Harmonisation; SOPs, standard operating procedures; QCDs, quality control documents; QMS, quality management systems; WMA, World Medical Association.

**About the authors**

Anu Gaur, PhD, Exec. MBA, MSRA, RAC (US & Global), is a senior-level US and global regulatory affairs strategist leader, and a graduate teaching faculty for graduate degree program, master of science in regulatory affairs (College of Professional Studies; CPS) and master of science in biotechnology (College of Science); and non-teaching faculty affiliate for Graduate School of Education (CPS), at Northeastern University,
Andrea Zobel, PhD, Dipl Biochem, holds a diploma in biochemistry from the Freie Universität Berlin and a doctorate degree from the Max-Planck Institute for Molecular Genetics. Her scientific career includes 12 years’ research in gene technology, pharmacology, and preclinical development in academia and biotech companies. She joined the clinical research industry in 2004, with positions in clinical supply management at Parexel; pharmalogistics provider Marken; and, from 2018 to 2021, in the role of the global head of the Parexel Academy. She is an active member of the ISPE (International Society of Pharmaceutical Engineering). Zobel can be contacted at andreazobel@web.de.

Bettina Merz-Nideroest, MPharm, graduated from the Swiss Federal Institute of Technology in Zurich with a master of science degree in pharmaceutical sciences and is a qualified pharmacist in Switzerland and Germany. She started her career as representative head of the sterile manufacturing department in the pharmacy of the University Hospital in Zurich. Merz-Nideroest joined Parexel in 2004 after relocating to Berlin and held different positions within the regulatory and clinical department, before joining the Parexel Academy in 2012. She is an expert in and lecturer on GCP, guidelines and regulations, approval processes, essential documents, and ethical considerations in clinical research. Merz-Nideroest can be contacted at bettina.merz@t-online.de.


References


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Planning for a clinical trial application

In recent years, global clinical trials have become standard, and for a good reason. In broad terms, expanding clinical trials across the world provides a better opportunity for demonstrating the true impact of an investigational drug. Global clinical trials offer key advantages to patients and industry, but smaller companies may be hesitant to participate in global trials, wondering if the inevitable challenges outweigh the benefits. The key considerations in designing a global clinical trial are selecting the most appropriate trial sites with a representative patient population, choosing to work with the right partners and staying stay up-to-date with the changing regulatory and clinical landscape. In this article, the author discusses planning global clinical trials, from choosing the countries through to preparation of a global dossier and submission of clinical trial application.

Introduction
Clinical trials are prospective, organized, systematic exposures of patients to interventions of some kind (e.g., drug, surgical procedure, dietary change). Clinical trials advance through four phases to test a treatment, find the appropriate dosage, and look for side effects. The health authority typically requires phase 1, 2, and 3 clinical trials to be conducted to determine whether the intervention can be approved for use. It is important for clinical trials to have participants of different ages, sexes, races, and ethnicities to have much wider applicability when the drug is in market.1 Over the past two decades, globalization of clinical trials has increased steadily for a number of reasons, for example: investigators have access to a greater number of willing, well-characterized, and often treatment-naïve participants, resulting in expedited enrollment; the availability of qualified local investigators eager to conduct trials; enhanced capacity of international sites; and the lower costs of conducting trials in developing countries.

Economic incentives to site trials in developing economies also stem from the significant increase in clinical trial costs in developed countries, such as the US and EU member states. In addition, national regulations increasingly require local, in-country study data to demonstrate a medicinal product or device is efficacious and safe in that country and thus across racial and ethnic groups. These regulations propel multinational pharmaceutical companies to consider involving these multiregional sites early in any drug development program.2,3 Despite the rise in clinical trials globally, conduct of such trials is particularly challenging in developing countries because of the relative scarcity of healthcare resources, the unavailability of appropriate medical care, and an inadequate infrastructure.
Globalization attracts resources to participating countries, to provide standardized clinical trial conduct and procedures and to train investigators and their teams.3

Choosing the countries
Many factors should be taken into account when selecting countries in which to conduct clinical trials, including:

- The ease of recruiting patients;
- The ease of recruiting qualified medical staff;
- Applicability of data (e.g., ethnic heritage might be a consideration);
- Regulatory requirements (e.g., a country may refuse to import a drug essential to the trial);
- The efficiency of the approval process;
- The resources already available (e.g., a regional hospital providing specialized equipment and a pool of physicians/patients);
- The market potential of the country (i.e., whether individuals will be able to access the medication or treatment after it is approved); and
- The standards of care acceptable for the study in regard to integrity and consistency of data.

Prior regional experience by the clinical research organization and/or research team is essential in finding a site because a network of former relationships can help ease every step of the clinical trial process, including recruitment, validation of physician credentials, and regulatory approvals.4

In choosing the countries in which to conduct global clinical trials, the regulatory professional should bear in mind that a global trial’s costs grow as the number of participant countries increases. Thus, it is important to establish the right balance between having a larger number of participant countries to enhance recruitment and facilitate approval and controlling the research costs.

Global dossier
Most clinical trial application (CTA) requirements, around the world, are based on requirements of the US Food and Drug Administration (FDA) or European Medicines Agency (EMA). Once those requirements are understood, applications in other countries can be similar, taking individual country-specific documentation into account (e.g., notarized copies of business licenses, draft case report forms, etc.).

The first step is to assemble a global dossier. A global dossier is not too different from the US investigational new drug (IND) application, because most commercial CTAs use the common technical document format preferred by the FDA. In addition to the IND, investigational medicinal product dossier, or CTA, completing the global submission will require collecting and making available the following:5,6

- Cover sheet (Form FDA 1571), including, but not limited to, sponsor contact information, investigational product name, application date, clinical investigation phase(s) to be conducted, and commitment that the ethics committee (EC) will conduct initial and continuing review and approval of each study proposed in the investigation.
- Table of contents
- Introductory statement and general investigational plan
- Master informed consent form (typically, if a country follows the International Council for Harmonisation [ICH], the same global requirements apply)
- Investigator’s brochure (IB)
- Protocol
- Protocol signature page
- Chemistry, manufacturing, and control data
- Pharmacology and toxicology data
• Previous human experience with the investigational drug
• Financial disclosure
• Letter of delegation of responsibilities/power of attorney
• Advertising
• Qualified person review and sign off (EU only)
• Data protection declaration (EU only)
• Case report forms (typically, draft acceptable)
• Data Safety Monitoring Board charter/Independent Data Monitoring Committee (typically, draft acceptable)
• Clinical supply labels in country-specific language
• Letter of acceptance of study from another country (if available), or letter or rejection from an EC (if applicable)

Ethics committee
The primary scope of information assessed by the EC (referred to as an institutional review board [IRB] in the US) relates to maintaining and protecting the research participants' dignity and rights and ensuring their safety throughout their participation in a clinical trial. The EC must also pay special attention to reviewing informed consent and protecting the welfare of certain participant classes deemed to be vulnerable. In addition, the EC is responsible for ensuring a competent review of the research protocol, evaluating the possible participant risks and expected benefits, and verifying the adequacy of confidentiality safeguards.

Clinical supply labels
Clinical supply products must be appropriately labeled in accordance with the following principles:
• Ensuring protection of the participant and traceability,
• Enabling identification of the product and the clinical trial,
• Facilitating proper use and storage of the product, and
• Ensuring the reliability and robustness of data generated in the clinical trial.

Determining clinical supply label requirements and translations can be very time consuming. The regulatory professional must first develop a table of what each country requires on the outer and inner packaging (bottle or vial) for both active study drugs and placebo (alternatively, Tarius or Cortellis cross-country tables can be used to help plan and manage this task). Then, the regulatory professional needs to determine requirements for a final label template, in each country's language. The label text must be translated, back-translated, and certified. The labels then are printed, checked against the certified translation for quality assurance, and the drug finally can be labeled. This entire process can take 3 to 6 months, depending on a range of factors, including time taken to compile initial requirements, translation time, printing, quality assurance, and time taken to schedule investigational material labeling. Any error on the final printed label (which can happen with a variety of languages and their unique characters) can set back a clinical program by several months.

The investigational product must be coded and labeled in a way that protects the blinding, if applicable, and also must be suitably packaged to prevent contamination and unacceptable deterioration during transport and storage.

Further, innovative approaches and technology have been implemented to manage clinical trial investigational product and auxiliary product traceability and accountability. For example, computerized technologies, such as interactive voice response systems or interactive web response systems, have been used to manage randomization, investigational product accountability at trial sites, dose titration, emergency unblinding and expiry date updating for clinical trials. Therefore, a measured degree of flexibility has been included in the regulations to allow alternative approaches to the labeling requirements, provided the labeling principles are not compromised.

Document translations
Once a company decides to conduct clinical trials in a country other than its home market, key clinical documents often require translation. Most documents will need to be certified translations (translated into another language, translated back, and reviewed against original documents to ensure the original intent has
not been lost). A certified translation will be accompanied by signed and dated documentation from the translator, identifying the document translated (stating the original language). Documents typically needing translation include:

**Before trial initiation**
- Protocol synopsis
- Protocol (typically in countries where a formal IND is not submitted)
- IB (typically in countries where a formal IND is not submitted)
- Informed consent form
- Patient diary or questionnaires
- Clinical supply labels
- Questions from regulators/answers from sponsors
- Ministry of health approval letters
- EC approval letters
- Investigators' Form 1572s and curriculum vitae (CV)
- Instructions for automatic randomization

**After trial initiation**
- Serious adverse events
- Annual reports
- Notice of study discontinuation or close-out
- Additional ministry of health or EC communication – for protocol amendments or IB

**Maintaining the submission**
After all of the above documents have been created, collected, and notarized, and the initial submission has been made, the work has just begun from a regulatory perspective. The submission now needs to be maintained. Here are the types of submissions required to support the submission:

**Serious adverse events**
Serious adverse events (SAEs) need to be reported in every country, meeting ICH or local ministry of health requirements. Some of the reporting challenges are:

- **Different forms in different countries.** In the US, SAEs need to be reported on MedWatch FDA Form 3500A, whereas the rest of the world uses the Council for International Organizations of Medical Sciences (CIOMS) form (except Canada, which uses the adverse drug reaction form).

- **Distribution.** Some countries and sites require paper SAEs, whereas other sites, ECs, and countries require electronic SAEs, which means converting the CIOMS form into XML and obtaining email addresses.

- **Timelines.** All SAE reporting timelines need to be met, even though there are different forms, timelines, and submission standards.

**Annual and quarterly reports**
Annual reports or development safety update reports are required in all major countries; the due date depends on the IND effective date and the EudraCT registration date, respectively. The IND effective date or date of first EU approval typically is known as the international birthdate, which establishes the date for annual report submission. For European countries that are not part of the EU, the annual report is due on the anniversary of the first site’s approval. Sometimes, countries allow sponsors to coordinate an annual report with only one or two data cuts needed to prepare the reports, but that is not always the case. This means the sponsor has to coordinate data analysis on an almost monthly basis to write annual reports for multiple countries. In addition, some EU and Eastern European countries require both quarterly safety reports and annual reports.

**Final report**
An investigator must provide the sponsor with an adequate report shortly after completing participation in the investigation. There is no specific timeframe stipulated for report completion.

The investigator or institution should provide the EC with a summary of the trial’s outcome and supply the FDA or the health authority with any additional report(s) required.

The sponsor or its principal investigator must submit results for applicable investigational product clinical trials to ClinicalTrials.gov no later than 1 year after the study’s completion date.
Submitting a CTA

The sponsor is responsible for submitting a CTA or IND application. Institutional EC review of the clinical investigation may be conducted concurrently with the FDA’s IND or health authority CTA review. However, EC approval must be obtained before the sponsor is allowed to initiate the clinical trial.5

To complete the IND application package, the sponsor must provide the following information in paper format or electronically:

- Cover sheet (Form FDA 1571), including, but not limited to: sponsor contact information, investigational product name, application date, clinical investigation phase(s) to be conducted, and commitment that the EC will conduct initial and continuing review and approval of each study proposed in the investigation.
- Protocols
- Chemistry, manufacturing, and control data
- Pharmacology and toxicology data
- Previous human experience with the investigational drug

Multicenter, or cooperative research, studies

In regard to multicenter clinical studies, which were required to comply with the revised Common Rule, all federally funded or sponsored institutions located in the US and engaged in multicenter research must use a single EC to review that study, known as the EC policy. This policy will streamline the review process and eliminate duplicative reviews. Exceptions to the requirement include when multiple EC review is required by law (including tribal law) or for research in which any federal department or agency supporting or conducting the research determines that the use of a single EC is not appropriate.

The National Institutes of Health (NIH) issued a final policy, effective 21 January 2019, that was designed to complement the revised Common Rule. The final policy required all institute-funded multicenter clinical trials conducted in the US to be overseen by a single EC, unless prohibited by any federal, tribal, or state law, regulation or policy.

Data safety and monitoring boards are also specifically required for NIH-funded multisite clinical trials, including interventions that involve potential participant risk.6

Protocol amendments, IB updates, and informed consent modifications

Each time a protocol amendment is made, the updated protocol and master informed consent form has to be sent to both the ministry of health and the EC, and the site will need to wait for an opinion from both before implementing the amendment. Whether the protocol is a substantial or administrative amendment will determine the review timeline.

IBs need to be reviewed on an annual basis for updates. If an update is made, it must be submitted to the sites, ministries of health, and ECs.

Shelf-life extension

If an investigational product expires during trial conduct, a shelf-life extension has to be filed. This submission can include: extended release statement, stability tables with stability data, and an extension justification memo stating the material will be good for another 3, 6, or 12 months, or a new study drug will need to be exchanged for the old material. Either way, this information will need to be submitted to countries requiring this update, and there often is a period of 28–60 days for reviewing this information before the material with the new expiry date or the new material can be used. If the shelf-life extension or information on the new lot is not submitted or reviewed in a timely manner, enrollment in the study could be halted until this has been resolved.

IBs need to be reviewed on an annual basis for updates. If an update is made, it must be submitted to the sites, ministries of health, and ECs.
In addition, new expiration date labels will need to be printed and the drug packages over-labeled at the site. The over-labeling process will need to be tracked to ensure all sites have received the updated labeling.

**Form 1572 and financial disclosure updates**

Assuming the study is going to be conducted under a US IND, if investigational site information changes, then Form 1572 needs to be updated and submitted to the sponsor in a timely manner. Some clinical research associates prefer to update Form 1572 at the end of the study. However, that is not acceptable, because the information can change many times during the study, and those changes need to be captured. In addition, any changes in financial disclosure information will need to be captured on a new financial disclosure form and evaluated to see if it affects the final study analysis (an additional, separate efficacy analysis might need to be conducted for investigator(s) who have exceeded financial disclosure limits). In addition, a final financial disclosure form will need to be submitted no later than a year after the study ends.

**Maintaining the US IND – paperwork required**

As with most investigator submissions, the sponsor needs to submit Form 1572 and the physician’s CV. (For some products, the IRB approval letter and informed consent form also need to be submitted, depending on the product and FDA reviewing division.) For studies conducted under a US IND outside the US, the following should be submitted:

- Form 1572 (in English)
- Investigator CV (in English)
- EC letter (if required) in native language, English translation, and a certified translation certificate
- Approved informed consent form (if required) in English and a certified translation certificate

**IND/investigational product supply, storage, and handling requirements**

The sponsor also must supply the investigator(s)/institution(s) with the investigational product, including the comparator(s) and placebo, if applicable. The sponsor must ensure the following:

- Investigational product quality and stability over the period of use
- Investigational product manufactured according to any applicable good manufacturing practices
- Proper coding, packaging and labeling of the investigational product
- Records maintained for investigational product document shipment, receipt, disposition, return and destruction
- Acceptable storage temperatures, conditions and times for the investigational product
- Timely delivery of the investigational product

**Record requirements**

The sponsor and the investigator(s) must retain the clinical investigation records and reports for 2 years after a marketing application (known as a new drug application) is approved for the investigational product; or, if a new drug application is not approved, until 2 years after shipment and delivery of the investigational product is discontinued for investigational use, and FDA has been so notified.

**Conclusion**

Conducting clinical trials in multiple countries is no small feat for the clinical or regulatory team, which not only supports ongoing maintenance but acts as the gatekeeper for initiating trials. Planning is essential not only to the trial initiation, but also maintenance. Mapping out all the required documentation, through
the regulatory professional’s own knowledge, with help from a contract research organization, or by using Tarius or Cortellis cross-country tables early, will help navigate the global clinical trial process with minimal delays to first patient enrolled.11,12

**Abbreviations**


**About the author**

Sharry Arora, MPharm, is clinical and marketed regulatory project lead with around 14 years of experience and expertise in providing global regulatory support for submission strategy and planning of all stages of product development including conceptualization, development, filing, approval and commercialization. She can be contacted at sharry.arora@novartis.com.

**Acknowledgment**

This article is based on a chapter in the second edition of Global Pharmaceutical and Biologics Regulatory Strategy. The reference for the chapter is: Arora S. Clinical trial application planning [Chapter 9]. In: Sietsema WK, Meacham MM, eds. Global pharmaceutical and biologics regulatory strategy. 2nd ed. Rockville, MD: Regulatory Affairs Professionals Society; 2020:99-106.

**Citation**


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This article provides an overview of Health Canada’s plans to modernize its clinical trials regulations and enhance health care agility in the regulatory framework for its health care products by making regulations more flexible and adaptive to innovation. The author discusses how clinical trials in several health care product lines can be modernized and looks at how lessons learned from the COVID-19 pandemic experience can help set up a more flexible regulatory framework that is better aligned with international standards and practices. She concludes that closer alignment with international, risk-based approaches and enabling novel clinical trials design will increase treatment options and product access for Canadians.

Introduction
The health care context is rapidly changing as products such as artificial intelligence, advanced cell therapies, and 3D-printed bioproducts are becoming more complex and personalized. Even as Canadians are demanding faster access to innovative products and seeking greater engagement on decisions about their health, this growing range of more complex products is accompanied by a wider spectrum of risk. At the same time, the COVID-19 pandemic, now entering its second year, has both provided an opportunity to test some agility measures and reinforced the need for greater agility in health care, particularly in developing health care products, revising clinical trial frameworks, and providing increasing transparency.

Responding to the calls for agility and modernizing clinical trials predate COVID-19. Since 2017, Health Canada has introduced a range of regulatory modernization initiatives. Progress has been made through efforts such as the Regulatory Review of Drugs and Devices, the Self-Care Framework, and the Medical Devices Action Plan. To enhance regulatory agility in support of innovation and economic growth, in 2018, the Health and Biosciences Economic Strategy Table highlighted additional opportunities. Health Canada also consulted a range of stakeholders and has developed a roadmap to achieve greater regulatory agility. Finally, the Government of Canada’s 2019 Budget included funding of C$120 million over 5 years to support modernization of clinical trials. Bill C-97 provided legislative powers to help in that effort.

One important aspect of the drive to modernize is the need to provide greater flexibility in clinical trial design and proportional oversight based on risk. Better access to clinical trials and greater information transparency are also key.
Why modernize clinical trial regulations?

Modernizing clinical trial regulations in Canada will create an environment that is more supportive of innovative clinical trials. Currently in Canada, the roles, responsibilities, and authorities related to trial conduct and design could be better defined, and the publication of clinical trial information relies on voluntary measures. Some requirements vary across product lines and internationally, food trials are not enabled, and regulatory inflexibilities may be limiting or slowing innovation and possibly preventing some clinical trials from coming to Canada.

Taking the aforementioned issues into consideration, there are three overarching objectives for modernizing the regulation of clinical trials in Canada:

- Continue to ensure the protection of research participants;
- Increase research and development through clinical trials in Canada; and
- Increase confidence in the integrity of Canadian clinical trial data.

COVID-19 and the need for ‘agile’ regulations

Before the pandemic, in 2018–19, Health Canada’s review of the health and biosciences sector found that oversight for clinical trials may be constraining growth and suggested committing to modernizing clinical trial regulations across product lines.

The pandemic has required its own agility and made it additionally clear that clinical trial regulations require modernization. Calls for increasing agility have come from government and stakeholders, who have asked for agility in enabling trials and patient participation, reducing unnecessary administrative burden, and advancing greater domestic and international co-ordination.

In May 2020, well into the early stages of the pandemic response, Health Canada introduced some agile concepts in clinical trial modernization through an Interim Order (IO) to better facilitate COVID-19 medical device and drug trials. Guidance on conducting clinical trials during a pandemic was also introduced, specifically calling for the regular sharing of information related to COVID-19 clinical trials.

Key proposed changes

A modernized and COVID-19 driven clinical trial framework offers 6 key changes:

- A new, risk-based approach to clinical trials,
- Streamlining across product lines,
- Lifecycle authorization for conducting clinical trials,
- New registration and disclosure of results,
- International alignment with good clinical practices, and
- Better health system efficiencies, such as those that can be achieved through decentralization of trials

Changes to the Food and Drugs Act, made in 2019, will also enable future regulatory changes.
An important change is the authority to authorize and oversee clinical trials and products within the trial through the product’s lifecycle. This step can enable a single authorization for trials involving different product lines and allows for cancellation or suspension of part of a trial. Another legislative change will make it possible to tailor authorization and oversight to the risk of the trial or products by lightening labelling and record keeping requirements for studies involving new uses for already approved products (when supported by appropriate evidence), or by adding terms and conditions to manage risk and uncertainties across the trial lifecycle.

Accessibility and transparency are important concepts in health care today. Subsequently, modernization of clinical trials will also require registering clinical trial information in a publicly accessible registry and disclosure of trial results.

**Proposed steps forward for product lines**

When modernizing and increasing the agility of clinical trial regulations, four product lines—human drugs, medical devices, natural health products, and food—require their own risk-based compliance and enforcement regimes.

For example, human drug product lines currently have unnecessary requirements for low-risk trials that are not suited to more complex trials, which could be remedied by increasing regulatory agility to address different types of clinical trial applications. For medical devices, many investigational trials are currently out of step with their international counterparts, which could be addressed by enabling investigational testing by independent researchers and health care professionals. The approach to clinical trials for nonprescription drugs and natural health products warrants greater alignment with other types of trials, and could benefit from faster approval timelines. Finally, the agri-food industry should be allowed to conduct clinical trials for infant formula and other foods meant for special dietary use within Canada.

**COVID-19 – Lessons learned and opportunities**

The COVID pandemic has proven an important driver for modernizing the clinical trials process and has shown that increased agility in the health care system can save lives. It is now up to clinical trial sponsors and regulators to leverage those lessons and recognize that this public health emergency also offers profound and unique opportunity. The IO reflects some key concepts that draw on a wider vision for the broader modernization of clinical trials. They include:

- Developing a new risk-based approach aligned with the market status of drugs.
- Adding terms and conditions to the authorization of drugs and devices.
- Shifting from a default No Objection scheme to new authorities to approve drug trials.
- Broadening sponsorship for a medical device trial, redefining who can conduct a trial, and who can act as a qualified investigator in drug trials.
- Gain the ability to suspend or cancel part of a trial.

Taken together, these efforts create a new, risk-based approach, streamlined across product lines. They are a step towards developing lifecycle authorization for clinical trials; establishing new registration and disclosure requirements; implementing international alignment; decentralizing trials and creating health system efficiencies; and enabling alternate means of informed consent. Some of these flexibilities are specific to the current pandemic and will help prepare for the next one, as well as to ensure regulations are more responsive to a rapidly changing health environment.

**Back to the future**

Clinical trial modernization requires ongoing consultations and forward thinking and planning for 2022 and beyond. While the 2020 Interim Order introduced agilities for COVID-19 clinical trials, leveraging lessons learned from the IO will be important for the future regulatory cycle, involving policy development, stakeholder engagement, publishing consultation reports, proposing amendments and, finally, publishing new regulations.

**Conclusion**

Canada is poised at the beginning of a five-year clinical trial modernization path that will support research and innovation, which is the first step in developing new
health products for Canadians. Modernization means developing more flexible, risk-based regulations that could allow not only for more trials, but for trials with a greater representation of patients in both national and international studies. This means creating greater alignment with international, risk-based approaches and enabling novel clinical trial designs, which could increase treatment options and product access for Canadians.

Modernization also means strengthening participant protections and increasing confidence in data. Future consideration for how a revised framework can reflect the evolving health care product environment is crucial, as is incorporating lessons from the COVID-19 pandemic and enabling and enhancing patient participation. The use of virtual/remote technologies to establish trial sites and patient participation, applied by necessity during COVID-19, should not only be a new normal, but refined to be even more useful, efficient, and efficacious.

Finally, modernization means that all stakeholders will continue to be more engaged – from framework design to function – as clinical trial modernization moves through the key stages from development to implementation.

About the author

Tanya Ramsamy, PhD, was the associate director of the Office of Clinical Trials, Therapeutic Products Directorate, Health Products and Food Branch, Health Canada. She has a doctorate degree in biochemistry from the University of Ottawa. Ramsamy can be contacted at tanya.ramsamy@canada.ca.

Acknowledgment

This article was adapted from a presentation given at the 2020 RAPS Convergence on 14 September 2020. Randolph Fillmore assisted in the preparation of the article. He can be reached at flasciencewriter@gmail.com.

Citation


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The Canadian application process and alternate pathway for COVID-19–related trials

Mukesh Kumar, RAC

Melanie Oakley

This article offers an overview of the clinical trial application process and guidance on the regulatory obligations pursuant to Part C, Division 5, of the Food and Drug Regulations for Clinical Trials Involving Human Subjects in Canada. The authors focus on clinical trial applications only for biologics (schedule D) and pharmaceuticals (schedule F). They provide information on a range of clinical trial submission requirements and communication with Health Canada’s relevant directorates and offices.

Introduction

The Health Products and Food Branch (HPFB) of Health Canada is the scientific and regulatory authority for health products and food in Canada.1 The investigational product classification for pharmaceuticals or biologics is designated by the directorate within HPFB, which will review and authorize the clinical trials.2 Clinical trial inspections are overseen by the Regulatory Operations and Enforcement Branch (Figure 1).

Part C, Division 5, of the Food and Drug Regulations (FDR), which came into effect on 1 September 2001, provides the regulatory guide and framework for the conduct of clinical trials in humans. Health Canada issued the guidance document, which incorporates International Council for Harmonization (ICH) E6(R2) Addendum fundamentals on good clinical practice and ethical and scientific quality standards for trials with human participants.3

Except for phase 4 studies, clinical trial sponsors must submit a clinical trial application (CTA) to Health Canada for authorization to sell or import a drug for the purpose of a clinical trial. CTAs are required for trials using drugs that are not authorized for sale in Canada, as well as trials using marketed drugs in which the proposed use of the drug is considered “off label.” This includes marketed drugs being used for a nonapproved indication or in a different target population than that for which it is approved, and/or if the route of administration or dosage regimens are outside the parameters of the notice of compliance (NoC) or drug identification number.

Health Canada must review the submission package and issue a no-objection letter (NOL) before initiation of a clinical trial or implementation of a CTA amendment (CTA-A). A CTA-A must be submitted after the initial CTA if any substantial changes are made to the initially approved protocol or quality (chemistry and manufacturing) information. Importation of investigational products may not occur until the sponsor has received the NOL.

CTAs should be sent to one of two review directorates within the HPFB of Health Canada. Pharmaceuticals are reviewed by
Regulations require clinical trial sponsors located outside of Canada to designate a senior medical or scientific officer who resides in Canada to represent them. The officer must sign a specific attestation related to the trial, for example Appendix 3 of the HC/SC 3011 Drug Submission Application Form, for every CTA/CTA-A submitted to Health Canada.

**Clinical trial application format**

Health Canada has been accepting regulatory submissions in the electronic common technical document (eCTD) format since 2004. The eCTD format allows for an electronic method of exchange, review, and management of health product information, but it requires the Common Electronic Submission Gateway (CESG) to manage regulatory transactions securely. Electronic documents are uploaded into the Health Canada viewing tool upon receipt. For many stakeholders, access to the CESG is not an option, and they may submit in “non-eCTD, electronic-only” format. CTA submissions made in non-eCTD format are provided to Health Canada on a CD-ROM and sent via courier or email. Non-eCTD submissions must include a cover letter, in both electronic and paper format, to identify the content of the submission. Paper submissions are no longer accepted.

The CTA is composed of three parts, or modules, in accordance with the CTD format:

- **Module 1** contains the administrative and clinical information about the proposed trial.
- **Module 2** contains quality (chemistry and manufacturing) summaries about the drug products to be used in the clinical trial.
- **Module 3** contains any additional supporting quality information (if applicable)

Alternately, Health Canada accepts quality information in EU Investigational Medicinal Product Dossier (IMPD) format, which can be included in Module 2. For CTAs to the TPD, a quality overall summary with the introduction section should be submitted along with the IMPD.

**Folder structure**

The content of the electronic media should be organized into folders according to a set structure (**Figure 2**). There are no requirements for file-naming conventions. However, Health Canada recommends that the file names be kept as brief and as meaningful as possible. Files should not be password protected and the PDF is the recommended format for electronic documents. PDF files should also be properly bookmarked.

In line with Figure 2, the CTA includes two Canada-specific summaries:

- **Protocol Safety and Efficacy Assessment Template (PSEAT).** A protocol synopsis in the defined format of a PSEAT should be submitted. This
requirement is for TPD only, and, although it is not a requirement for BRDD, it is recommended to submit a PSEAT to facilitate review. The PSEAT is required for the initial CTA only.6

- **Module 2 Quality Overall Summary.** Health Canada has made available three templates, one for each trial phase (1, 2, and 3). This is required for CTAs sent to TPD only.

### Transmission of electronic data

CTAs and CTA-As can be submitted on electronic media in the form of a CD-R or a DVD, usually sent via courier. The submission must be organized in accordance with the current electronic specifications as outlined in the Health Canada issued guidance document for preparing submissions in the non-eCTD electronic-only format.5

CTA notifications (CTA-Ns) should be provided to Health Canada via email and sent to the appropriate Directorate.

Regulatory transactions provided by email should meet the following requirements:

- The maximum email size accepted by the corporate mail server is 20 MB; anything larger should be sent on media.
- The regulatory transaction should be organized in folders and provided as a zipped file.
- The body of the email should contain only the zipped regulatory transaction. No other documents or related information should be included.
- Zipped files and documents contained in the email should not be password protected.

In general, CTA and CTA-As are to be submitted on electronic media, and CTA-Ns are sent via email.

### Clinical trial application-review process

#### Pre-CTA meeting

Applicants have the option to apply for a pre-CTA consultation meeting with Health Canada to obtain guidance on complex issues that may arise during the application or review processes. Requests for pre-CTA meetings must be submitted in writing and should include a brief synopsis of the proposed study and a list of preliminary questions to be addressed by the appropriate directorate. Once the request is approved, the directorate will confirm the meeting date and the number of copies of the pre-CTA information package to be provided 30 days before the confirmed meeting date.

After the pre-CTA meeting, the sponsor must prepare a written summary of the discussions, which will be added to the central registry file for the drug. The CTA should include a copy of the meeting record.

#### Screening process

All CTAs are subject to the 30-day default period from the date of receipt of the completed application. The
The directorate will issue an acknowledgment letter, or acknowledgment of receipt (AoR), to indicate the start of the review period and that Health Canada is in receipt of a complete application. A control number will also be issued for the application on the AoR.

All CTAs and CTA-As will be screened for completeness. If deficiencies are identified at screening, these will be addressed through a screening clarification request (issued by the TPD) or a screening information letter or process hold (issued by the BRDD) sent via email or fax. There is no timeframe specified for the TPD, but the “review clock” will stop until a satisfactory response is received from the sponsor. Sponsors should respond to screening information letters issued during screening within 2 days for the BRDD and, if a process hold is used, the review clock is stopped and a response is expected within 7 days.

A screening rejection letter may be issued if the required information has not been included in the CTA or CTA-A, or responses to requests for clarification have not been received in a timely manner. If the sponsor wishes to resubmit the information later, the application may be withdrawn without prejudice and resubmitted as a new CTA or CTA-A.

**Review process**

During the review process, the sponsor is responsible for resolving issues identified by Health Canada. Sponsors must provide the requested information within 2 calendar days. A “not satisfactory notice”, or NSN, may be issued if significant deficiencies are identified during review of the CTA or CTA-A, or if a timely response to the information requested has not been provided. If the applicant wishes to resubmit the information and material at a future time, it will be processed as a new CTA or CTA-A and assigned a new control number as per the guidance on management of drug submissions.4

If the CTA or CTA-A is deemed acceptable, an NOL will be issued within the 30-day review period (Figure 3).

**CTA amendments**

CTA-As are submitted to Health Canada when there is a change to the information in the previously authorized application. This includes changes to the protocol and/or the quality information, or changes that affect the quality or the safety of the drug. CTA-As must be reviewed and approved by Health Canada before implementation unless there is imminent danger to the health or safety of clinical trial subjects. If the sponsor has to make an immediate change to the study protocol to protect patient safety, then Health Canada must be notified within 15 days after the date of implementation of the amendment and provide sufficient rationale and documentation to support the changes. A summary of changes to the protocol, as well as the rationale for each change, should be included.

A CTA-A must be filed when the proposed amendments to the protocol:
- Affect the selection, assessment, or dismissal of a clinical trial subject;
- Affect the evaluation of the clinical efficacy of the drug;
- Alter the risk to the health of a clinical trial subject;
- Affect the safety evaluation of the drug; or
- Extend the duration of the treatment.

Protocol changes should also be reflected in the updated informed consent form (ICF), if applicable. Copies of the tracked changes to the ICF should be included with the CTA-A submission.

**Quality amendments**

Sponsors must file a CTA-A or CTA-N for changes made to the quality summary of the drug in Module 2 or Module 3, if applicable. Examples may include, but are not limited to, the replacement or addition of a drug substance or product manufacturing site, changes to specifications for the drug substance or product, or shelf-life reductions related to stability concerns.

Because submission requirements differ between the BRDD and TPD, the applicant should reference the Health Canada issued guidance document for clinical trials4 for detailed information.

Similar to CTAs, CTA-As should be organized and numbered as per the CTD format and submitted via electronic media with a hard copy cover letter as per the specifications in the Health Canada guidance.
document on preparing drug regulatory activities in the non-eCTD electronic-only format. The screening and review timelines for CTA-As are the same as those for CTAs. If the CTA-A is deemed acceptable, an NOL will be issued within the 30-day review period.

**CTA notifications**

Changes to an application not meeting the criteria for CTA-As should be submitted as notifications within 15 days of the change. Notifications should be submitted electronically and may be implemented immediately after submission.

Notifications may include, but are not limited to:

- Changes to administrative information,
- Annual investigator brochure updates,
- Updates to the ICF that do not require a protocol amendment,
Changes to the protocol that do not affect the study design or safety of the participants,
• Changes to the quality information that do not affect the quality or safety of the drug, and
• Premature discontinuation of a trial.

CTA-Ns can be sent via email to the appropriate directorate in a zipped file with an accompanying cover letter.

Additional post-authorization, pretrial requirements
Research ethics board review
The proposed trial protocol/protocol amendment and the ICF must be reviewed and approved by a Research Ethics Board (REB) before initiation of a CTA or implementation of CTA-A. If the sponsor receives a refusal from another ministry of health (e.g., another country in a multinational trial) or ethics committee, then a notification should be submitted to Health Canada and the affiliated REB.

An REB attestation form, or a similar attestation, must be obtained and signed by the REB chair that approves the CTA/CTA-A at each site. The form should be retained at the sites and not submitted to Health Canada unless requested.

Qualified investigators
Only one qualified investigator (QI) is allowed per site. The QI must complete a qualified investigator undertaking form or develop similar documentation that meets the requirements of the regulations [C.05.012(3) (f)]\(^7\). The form should not be submitted to Health Canada unless requested.

CTSI form
A clinical trial site information (CTSI) form for each participating site should be submitted to the appropriate directorate before starting a clinical trial or implementing a CTA-A (applies to clinical amendments only). In addition, if there is a change in the site address, or if the REB with which the site is affiliated is changed, a new CTSI form should be submitted to Health Canada.

Lot release information (for biologics only)
Biologic lots intended for use in a clinical study are subject to a lot-release program requirement before the lot is used in a clinical study. Previously, all biologic lots used in a clinical study were subject to this requirement. However, as of 8 July 2020, this requirement is applicable only to:
• Biologics that contain human-derived excipients, such as human serum albumin; and
• Clinical trial lots that are released outside of the approved specification.\(^7\)

The “faxback form” should be signed by the sponsor or manufacturer and submitted to the BRDD, which will return the signed form to the sponsor within 48 hours. Once the sponsor has received the form, the specific lot can be used in the study.

Importation of clinical trials drugs
If the investigational product is imported, the importer should be authorized by the sponsor. The importer should be included in Appendix 1 of the application form (HC3011) and submitted to Health Canada. Importer information can be submitted with the initial CTA or later when determined.

Importation of additional drugs
For additional drugs (comparator, concomitant, and rescue medications) that have to be imported into Canada, a summary of additional drugs (SOAD) form must be submitted to Health Canada. A Health Canada official will sign the form and return it with the NOL. If the form was not submitted during the initial CTA, it should be submitted as a CTA-N before shipping the drugs to Canada. The signed SOAD form should accompany the shipment.

Labeling requirements
The investigation product should be labeled per section C.05.011 of the Food and Drug Regulations. The regulation applies to both inner and outer labels and commercially available products considered as investigational. Labels are not submitted to Health Canada unless requested.
Post-authorization, post-commencement requirements

Changes to previously authorized CTA
Changes to any information submitted as a part of the initial CTA should be submitted to Health Canada. The changes can be submitted as a CTA-A or CTA-N, as discussed earlier in this article, based on the type of change and its impact.

Premature discontinuation of a trial
A CTA-N should be submitted as soon as possible, but no later than 15 calendar days after such decision.

Resumption of a trial after discontinuation
A CTA-N should be submitted with the proposed re-initiation date if there is no change to the authorized study documents. In the event a protocol or quality information is amended to facilitate the continuation of the trial, a CTA-A may be required, depending on the nature of the changes.

Study completion/site closures
A CTA-N to the relevant directorate should be submitted in the event of a site closure or completion of a study.

A study is considered to have been completed after the last subject has complete the end-of-study visit, as defined in the protocol. This does not include study suspension, cancellation, or closure of the trial in Canada. The end-of-study visit is the final visit for study-related tests and procedures, including the capture of any final potential study-related adverse events.

Safety reporting
Health Canada should be informed in an expedited manner of any serious, unexpected adverse drug reactions, as described in the timelines as below:

- Neither fatal nor life-threatening, within 15 days after becoming aware of the information; or
- Fatal or life-threatening, within 7 days after becoming aware of the information. Submit as complete a report as possible within 8 days after initially informing Health Canada of the fatal or life-threatening adverse drug reaction.

Both investigators’ and sponsors’ causality assessment should be reported.

Updated investigator’s brochure
An updated investigator’s brochure, including all safety information and global status, should be submitted annually. If there is a determination that the brochure is not required, a CTA-N stating as much should be submitted.

Record retention
The sponsor is required to maintain complete and accurate records of all trial-related activities. The records are to be retained for 25 years. If any records are requested by the relevant directorate, they must be made available within 2 days.

An alternate pathway for COVID-19-specific trials
On 23 May 2020, an Interim order (IO) was issued regarding COVID-19–related clinical trials for medical devices and drugs in response to an urgent need for the diagnosis, treatment, mitigation, or prevention of COVID-19 (Table). The IO is a temporary measure that provides an alternate pathway to enable the initiation of clinical trials for potential drugs and medical devices for COVID-19 while upholding strong patient safety requirements and validity of trial data. The IO will be in effect until at least the fall of 2021.

Health Canada issued two guidance documents to support the IO:
- For drugs: Applications for drug clinical trials under this Interim order, and
- For medical devices: Applications for medical device clinical trials under this Interim order.

The guidance documents apply to COVID-19 clinical trials for pharmaceutical and biologic drugs (including blood and blood components) and medical devices, including combination products. Clinical trials are for phases 1 through 3 of medical device development. Radiopharmaceuticals (see Schedule C of the Food and Drugs Act), natural health products, Class I medical devices, and phase 4 clinical trials are not included in the IO.
The existing regulations and guidance for all clinical trials that are not COVID–19 related and are not in-scope would continue to apply.

Applicants for COVID–19 drug and medical device clinical trials can apply for authorization under one of the following:

- The IO pathway;
- Part C, Division 5, of the Food and Drug Regulations (current regulation); or
- Part 3 of the Medical Devices Regulations.10

The IO will reduce administrative requirements for assessing repurposed drugs for COVID–19, enable alternate means for consenting, and broaden criteria/definition of which health professionals are authorized to conduct clinical trials at remote sites.

### Table. Comparison of current regulations and interim order8, 11

<table>
<thead>
<tr>
<th></th>
<th>Part C, Division 5 (current regulation)</th>
<th>Interim order (for COVID–19 trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review period</td>
<td>30-day default authorization</td>
<td>Within 14 days, authorization for importation or sale of COVID–19 drug</td>
</tr>
<tr>
<td>Information request</td>
<td>Response within 2 calendar days</td>
<td>Response within 24 hours</td>
</tr>
<tr>
<td>Submission process</td>
<td>Mail CD-R/DVD to Health Canada</td>
<td>Via email, to: BRDD, <a href="mailto:hc.brdd.cta-dec.dmbr.sc@canada.ca">hc.brdd.cta-dec.dmbr.sc@canada.ca</a> TPD, <a href="mailto:hc.oct.smd-dgp.hec.sc@canada.ca">hc.oct.smd-dgp.hec.sc@canada.ca</a></td>
</tr>
<tr>
<td>Minor changes to authorized information</td>
<td>Submitted as CTA-N</td>
<td>Changes qualifying as a CTA-N can be implemented without submitting a notification</td>
</tr>
<tr>
<td>Who can conduct research? QI definition</td>
<td>The person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is (a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association; and (b) in any other case, a physician, and a member in good standing of a professional medical association. Per the above definition, the QI must be a physician or a dentist.</td>
<td>The person who is a member in good standing of a professional association of persons entitled under the laws of a province to provide health care under their license in that province and who: (a) conducts the clinical trial; or (b) in the case of a clinical trial conducted by a team, who is the responsible leader of that team (chercheur compétent). The definition is expanded to include other healthcare practitioners, such as nurses, pharmacists, and midwives.</td>
</tr>
<tr>
<td>Terms and conditions imposed on the authorization</td>
<td>Terms and conditions cannot be imposed or amended on the authorization.</td>
<td>Health Canada can at any point impose or amend terms and conditions on the authorization, e.g., requesting submission of periodic safety summary or of results of the first phase of a phase 1/2 study</td>
</tr>
<tr>
<td>Compliance and enforcement</td>
<td>Current regulations do not allow for discontinuation/cancellation of one arm of a study. The whole study should be cancelled or discontinued.</td>
<td>Enables suspension or cancellation of a part of or the entire study.</td>
</tr>
<tr>
<td>Labeling</td>
<td>Marketed product, if considered as investigational, should comply with labeling requirements under section C.05.011 of Division 5 of the FDR.</td>
<td>Commercial label acceptable.</td>
</tr>
</tbody>
</table>

**BRDD**, Biologic and Radiopharmaceutical Drugs Directorate; **CTA-N**, CTA-notification; **FDR**, Food and Drug Regulations; **QI**, qualified investigator; **TPD**, Therapeutic Products Directorate.
It is important to note that COVID-19 trials that had commenced before 20 May 2020 cannot be transitioned to the new pathway under the IO.

**Modernization of clinical trials regulations**

Clinical trial business models have evolved from the traditional linear clinical trial model (preclinical, clinical, and post-launch studies) as most of the innovative novel approaches are not suited under current regulations. For example, master protocols, such as basket trials and umbrella trials, are novel designs that facilitate evaluations of more than one investigational medicinal product and/or more than one type of indication within the same overall trial structure. To facilitate such evaluations, the study includes a master protocol/study and sub-protocols/studies, as required. Currently, Health Canada reviews CTAs on a per-protocol basis. In case master protocol trial designs are utilized, a separate CTA should be submitted for each sub-protocol. This leads to an increased regulatory and financial burden. To address such issues, Health Canada is proposing to amend the current clinical trial regulations to introduce a coherent risk-based approach for oversight of conducting clinical trials and enable increased flexibility in the safe development of innovative therapies. In addition, there are several other modernization initiatives Health Canada is proposing, including a reduced record retention proposal, from 25 years to 15 years, to better align with global regulators.

**Conclusion**

Canada continues to be an attractive destination for the conduct of clinical trials. With shorter approval timelines and considerably more universal submission requirements, the Canadian framework will continue to be an appealing option for pharmaceutical companies and research institutions to make significant investments in Canadian clinical trial health research.

**Abbreviations**

BRDD, Biologic and Radiopharmaceutical Drugs Directorate; CESG, Common Electronic Submission Gateway; CTA, clinical trial application; CTA-A, CTA amendment; CTA-N, CTA–notification; eCTD, electronic common technical document; EU, European Union; FDR, Food and Drug Regulations; HPFB, Health Products and Food Branch; ICH, International Council for Harmonization; IMPD, Investigational Medicinal Product Dossier; NoC, notice of compliance; NOL, no-objection letter; PSEAT, Protocol Safety and Efficacy Assessment Template; QI, qualified investigator; REB, Research Ethics Board; SOAD, summary of additional drugs; TPD, Therapeutic Products Directorate.

**About the authors**

Mukesh Kumar, RAC, is a regulatory specialist with PRA Health Sciences, with more than 6 years’ experience in the pharmaceutical regulatory sector. Kumar has experience in developing regulatory strategies and writing high-quality regulatory submissions (NDS, NDA, SNDS, CTA/CTA-A, 510(k)s) for drugs, biologics, and medical devices. He has a postgraduate certificate in Pharmaceutical Regulatory Affairs from Humber College, Canada. He can be reached at kumarmukesh@prahs.com.

Melanie Oakley has worked for more than 18 years in clinical research, mainly for large contract research organizations. She spent 8 years as a clinical research associate before moving to regulatory affairs, 8 years ago, while living and working in the UK. Oakley’s current role as a manager of global regulatory affairs at PRA Health Sciences includes preparation and submission of Canadian clinical trial applications. She can be reached at oakleymelanie@prahs.com.

**Acknowledgment**

The authors thank Daniel Mannix for his guidance and recommendations during the development of this article.


*This article is an updated version of an article published by Regulatory Focus on 4 August 2020.

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All websites last accessed on 22 February 2021, unless noted otherwise.


Initiating clinical trials in China: What foreign medtech companies need to do

This article discusses numerous recent changes in the regulation of clinical trials in China and proposes that Chinese clinical trials for medical device and in vitro diagnostic device (IVD) products are an increasingly viable option for non-Chinese companies of all sizes.

China’s regulatory framework
Most life sciences products, including medical devices and IVDs, sold in China are supervised by the National Medical Products Administration (NMPA). The agency uses a risk-based classification system with three classes, in which Class III is the highest-risk and requires the most regulatory scrutiny. (NMPA was known as the China Food and Drug Administration until its name was changed in 2018.)

Premarket approvals for Class II and Class III medical devices and IVDs in China will, by default, require clinical trials in support of the application dossier, unless the applicant can:
- Identify its product on the clinical trial exemption list,
- Provide sufficient information about a predicate device that is approved by NMPA, or
- Provide sufficient overseas clinical trial data.

The requirements are largely the same whether a company is a domestic or foreign applicant.

If clinical trials are required, non-Chinese companies often see this as a “show-stopper” for their China market entry. But this need not be the case. With an ageing population, rising prosperity, and government encouragement even before the healthcare-focused accelerations from COVID-19, the China healthcare market is attractive for foreign medical device and IVD companies.

Healthcare teams at Chinese hospitals are increasingly knowledgeable about, and open to, supporting clinical trials. Some provinces – such as Hainan, an island province off the south coast of China – have even developed specific solutions to try to attract global players into their hospitals to run certain trials.

China-based clinical trials are therefore an increasingly viable option for foreign companies of all sizes, although that may not have always been the case.²

This article discusses numerous recent regulatory developments encouraging the China clinical trial trend and outlines what foreign medical device and IVD companies should consider before initiating a clinical trial in China. The article does not address clinical trial regulations relating to drugs, but readers should be aware of a revised Drug Registration Regulation that took effect
on 1 July 2020, which makes changes to the regulation of clinical trials of pharmaceutical products in China.3

**Exempted and mandatory trials**

**Exempted**

Although the default position for Class II and Class III medical devices and IVDs is that they will require a clinical trial, the NMPA regularly issues lists of products it considers exempted from clinical trial requirements. At the time of writing, there were more than 1,000 Class II and 200 Class III medical devices and IVD product categories exempted from clinical trials. For those listed products, a greatly simplified clinical evaluation report is sufficient to support a premarket approval application.

The NMPA most recently updated the list of products exempted from clinical trials in China in January 2021, with the addition of 85 medical devices and 7 IVDs. The clinical trial exemption lists are available on the NMPA website.4

**Mandatory**

The regulator also expressly requires certain high-risk product categories to undergo clinical trials. This requirement will generally be stipulated in product-specific standards and guidelines.

- Clinical trials will generally be required for:
  - Devices in which there is a completely new design or new intended use;
  - Nonactive implantable medical devices not approved on the domestic or overseas markets;
  - Orthopedic and dental implants not been approved on the domestic or overseas markets, but where safety and effectiveness are not clear; or
  - Products approved in the overseas markets, but not for China, and where evidence on safety and effectiveness is not sufficient.

Examples of high-risk devices include implantable cardiac pacemakers, implantable blood pumps, and certain orthopedic implants.

**Overseas data**

Since January 2018, qualified clinical data collected outside China is permitted to form the basis of a clinical evaluation report in place of conducting a China-based clinical trial.5 This is even the case for devices the NMPA considers high risk, such as implantable pacemakers and heart pumps.

Data is qualified for the NMPA if it is ethical, legal, and scientific:5,6

- **Ethical principle.** This refers to the requirement that the collection of clinical data must have been approved by a local ethics committee, and the opinion of the relevant local ethics committee will need to be submitted to the NMPA as part of the registration dossier.

- **Legal principle.** This means the clinical trial must have been conducted in accordance with China good clinical practice (GCP) for medical devices,7 which is substantially similar to globally recognized GCP standards (in particular, ISO 141558), but with additional, China-specific requirements. China GCP became effective 1 June 2016. The protocol and planning of the trial will need to be submitted together with the registration application.

- **Scientific principle.** This refers to the requirement that the data are authentic, reliable, traceable, and nonselective. Complete clinical data will need to be submitted with the registration application.

On the basis of being authentic, scientific, reliable, and traceable, overseas medical device clinical trial data submitted by the applicant should at least include an ethical opinion review and approval documents; complete clinical trial protocol; and complete clinical trial report, which includes an analysis of the complete clinical trial data and the conclusions.

A guideline regarding overseas clinical data for IVD reagents is also currently being drafted and solicitations for comments from industry have been sought.9 Once effective, this guideline will provide additional guidance in respect of acceptance in premarket approval applications of IVD clinical data obtained outside of China.

**Trial initiation and notifications**

Since April 2019, preapproval to begin a clinical trial is no longer required for most devices. Instead, notice of
the trial is given to NMPA’s Centre for Medical Device Evaluation (CMDE), and if no response has been received within 60 working days, the trial can begin. This simplifies the previously required preapproval process. Instead of an approval notification, the NMPA’s website will display the approval number; the applicant’s name and address; and the name, model specification, structure, and composition of the medical device.

However, the CMDE will still require pre-approval for certain high-risk devices. These products are listed in the Catalog of Class III Medical Devices Requiring Clinical Trial Approval.

In addition, sponsors should still register their clinical trials with an online registry, such as the Chinese Clinical Trial Registry, before the first participant is recruited. The registry was established in 2005 and was assigned to the Ministry of Health of China to represent China at the World Organization of Health’s (WHO’s) International Clinical Trials Registry Platform in 2007. The minimum information to be registered is specified in the WHO Trial Registration Data Set, which is available on the WHO website. The registry record will be the only publicly available document on a trial until results from the trial are published.

**Hospital-based clinical trials**

China clinical trials must generally be conducted at two or more NMPA-approved hospitals and meet NMPA registration requirements. Class III IVD trials will generally require a multicenter trial with at least three clinical sites. Because top-tier hospitals in China are concentrated in the major cities, close consideration should be given to site selection to ensure duration and efficiency of the trial are optimized.

There is a tiered hospital system in China, with Level III A+ at the highest tier and Level I C at the lowest. The levels are determined by the Chinese government according to treatment ability, staff training, and research capability. Level III hospitals are generally selected for clinical trials and, for high-risk medical devices, the hospital should be at the highest level, Level IIIA.

A number of regulations have been issued in recent years, adding to the list of hospitals approved as clinical trial centers. The list of hospitals is available on the NMPA website and includes the name, address, contact details, and level or tier of the hospital within China’s tiered hospital system.

**Key steps in the clinical trial process**

The key guideline that sets out much of the requirements for the clinical trial process is China’s Good Clinical Practice for Medical Devices (China GCP). It largely follows international GCP, although there are some local differences, such as requirements relating to consideration of ethnic differences of the local Chinese population.

Another Chinese-specific consideration is a requirement for any clinical trials involving genetic information to be registered with the Human Genetic Resources Administration of China, which should be factored into any relevant trial timelines for IVD or medical devices involving genetic data.

An outline of the key steps is set out in the accompanying figure. The clinical protocol or plan should be drafted in parallel to initial preparation and planning of materials and equipment. Some specific considerations about the protocol are discussed further below. Once the hospitals are selected and the plan finalized, ethics committee approval is required before trial initiation.
During the patient enrolment process, milestones of 10%, 30%, 60%, and 90% visit thresholds are common. Treatment, analysis, and data review are the critical stage of the process, but data follow-up and analysis, reporting, and site close-out are the scientific validation to the investigation. A reasonable timeframe from the author’s experience is 2 years although this can vary considerably depending on the product and the circumstances.

**Drafting clinical trial protocols**

The protocol design should strictly follow NMPA’s Medical Device Clinical Trial Design Guideline issued in January 2018. In addition:

- Devices that are brand new – that is, not yet approved in China or elsewhere in the world – must present supportive evidence from a small-scale feasibility study. Before completing the protocol for subsequent trials, a statistical analysis of the small-scale trial should be used to determine the sample size of those trials (Article 27, Decree No. 25).
- Ten specific types of documents must be provided to the ethics committee before a clinical trial can begin, including the researcher’s manual, proof of the experience of the researchers, and the forms used to recruit participants, among others (Article 17, Decree No. 25).
- The ethics committee should have at least five members with a diverse constituency, including representation from both genders, and medical and nonmedical members.
- Any changes to the trial protocol should be submitted...
to the ethics committee for ratification (Article 11, Decree No. 25).7

Additional information
The NMPA website has an English-language website with limited content, although the amount is expanding. In particular, China’s Good Clinical Practice for Medical Devices (Decree No. 25) is available on the website in English and is a helpful free resource giving guidance on the key requirements.7 There are also a variety of clinical research organizations and regulatory consultants active in the space with English language expertise.

Conclusion
China-based clinical trials are an increasingly viable option not only for large global medical device and IVD companies but also for medium and small-sized companies. Numerous regulatory developments relating to China clinical trials should clarify and encourage local China trials as requirements converge on international standards.

Abbreviations
CMDE, [NMPA’s] Centre for Medical Device Evaluation; GCP, good clinical practice; IVD, in vitro diagnostic device; NMPA, National Medical Products Administration.

About the author
Hamish King, LLB, RAC, is COO at Cisema, a contract research organization and turnkey regulatory affairs service provider for the Greater China market. He is currently based in Hong Kong where he specializes in NMPA registration of medical devices. King, admitted as a lawyer in New South Wales, Australia, and Hong Kong, was previously a solicitor with Magic Circle firm Linklaters and has 9 years’ experience in the legal and regulatory fields. He graduated from the University of Sydney with BA honors degree and law degree. King has a close interest in the regulatory implications of digital healthcare and AI applications and is a member of RAPS (with RAC certification), APACMed, and a CFA Charterholder. He can be contacted at hamish.king@cisema.com.


*This article is an updated version of an article published by Regulatory Focus on 1 September 2020.

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