NSW Office for Health and Medical Research online CTN guidance
22 December 2015

The following is NSW OHMR's interpretation of requirements. This has not been endorsed by the TGA. Do not use it as a substitute for legal advice, where needed.

On 1 July 2015, the Therapeutic Goods Administration (TGA) launched the electronic clinical trial notification (CTN) scheme (Notification of Intent to Supply Unapproved Therapeutic Goods under the Clinical Trial Notification Scheme), which replaced the paper-based notification form. Per the TGA CTN scheme website, all CTNs must be submitted using the online form. In response to NSW stakeholder queries, the Office for Health and Medical Research (OHMR) has developed this guidance document in consultation with local research offices and other jurisdictions.

What are the primary differences between the online CTN and the former paper-based CTN form?

The primary differences between the two mechanisms include, but are not limited to:

- **Omission of signature declarations, and PI, HREC and Approving Authority declarations:** The online CTN form requires a declaration from the sponsor of the trial, which is completed by clicking an "accept" button. A written sponsor signature is no longer required. As well, the paper form's sections 2 (Principal Investigator certification), 3 (HREC certification), and 4 (Approving Authority [AA] certification) are no longer required for the sponsor's notification.

  The OHMR's guidance is that institutions are not required to continue to request and maintain paper CTN forms and signatures in addition to the online CTN.

  OHMR recommends that:

  (i) the HREC approval letter fulfils the documentation required to indicate HREC approval; and
  (ii) the Site Authorisation letter fulfils the documentation required to indicate Approving Authority approval.

- **Collection of additional data:** Per the TGA's 5 May 2015 presentation at ARCS Australia, the online CTN form collects additional data on the use of unapproved therapeutic goods in clinical trials to help identify clinical trial activities and trends within Australia. Data collected on the online CTN form that were not included on the paper form include: total number of participants to be enrolled; therapeutic area; date and reason trial completed; medication information such as formulation, intended use and information on animal excipients if relevant; specific device, biological and placebo details; free text fields for gene therapy and Genetically Modified Organism details; and, information on trials being conducted in other countries.

- **Direct linkage between the CTN system and TGA Business Services:** The online CTN form links directly with TGA Business Services (TBS), which enables trial sponsors to pay invoices online.

- **Change in fees and charges:** For new trials under the CTN scheme, the same fee applies for notifying a multi-site trial or a single site trial, providing the sites involved in the multi-site trial are declared simultaneously on the online CTN form. In addition, certain changes to an existing CTN (that has been acknowledged by the TGA) may incur a fee, such as:
  - Addition of a site(s)

- Changes to a previously notified site address
- Addition of new therapeutic goods
- Changes to previously notified therapeutic goods that creates separate and distinct goods

The full schedule of fees and charges is available here. As of 1 July 2015, a CTN costs $335.

How does the online CTN correspond with regulatory requirements?

By signing the online CTN sponsor declaration (full text at the bottom here), the sponsor acknowledges overall responsibility for the trial, and that "the requirements in regulation 12AD of the Therapeutic Goods Regulations 1990 (in the case of therapeutic goods other than medical devices) and regulation 7.5 of the Therapeutic Goods (Medical Devices) Regulations 2002 (in the case of medical devices) are complied with, including that the use of therapeutic goods in the trial must be in accordance with the Guidelines for Good Clinical Practice and the National Statement on the Ethical Conduct in Research Involving Humans published by the National Health and Medical Research Council, as defined in the Therapeutic Goods Regulations."

EXTERNAL SPONSORS – Commercial or Non-commercial

How can an HREC ensure that an external sponsor does not submit a CTN without HREC approval?

Essentially, it can't. However, if the sponsor does submit a CTN without first obtaining an HREC's final approval, then it is the sponsor who risks having made a false declaration to the TGA rather than the HREC.

The online CTN sponsor declaration acknowledges that "the approval of the goods for the trial has been given by the sponsor (if the sponsor is conducting the trial), or by the body or organisation conducting the trial for the sponsor, ***having regard to the advice of the ethics committee responsible for monitoring the conduct of the trial, on terms no less restrictive than terms advised by that committee,"*** and that "***the sponsor has not received advice from the ethics committee that is inconsistent with the continuation of the trial***" (emphases added). The sponsor thus assumes responsibility for assuring the TGA that HREC approval for the study has been received.

The OHMR recommends that HRECs and institutions establish local guidelines and checklists that recommend that external sponsors should not submit an online CTN until written HREC approval has been received. Institutions need not review CTN submissions (e.g. printed PDF or screen-shot copies of online submissions) particularly as contingencies of study approval. HRECs and institutions also are not required to request a copy of the TGA acknowledgement of receipt of a CTN from the sponsor, as acknowledgement has never been a requirement for a study to begin.

How can an Approving Authority ensure that an external sponsor does not include its site on a CTN without site authorisation?

The sponsor enters specific "trial site details" for each study site, including site name, address, expected site start date, site PI name and contact details, and HREC and Approving Authority contact details. However, neither the online CTN sponsor declaration nor the regulations reference the need for approving authority authorisation, and an approving authority written declaration is no longer required.

As noted above, the sponsor declaration acknowledges compliance with ICH GCP, which requires that a signed agreement between involved parties (including authorities, where required) and dated

documented approval of an ethics committee be on file before a clinical trial formally starts (ICH GCP E6 section 8.2).

It is not a regulatory requirement for a sponsor to receive written site approval/ site specific authorisation before adding each new site to the online CTN. It would be reasonable for an institution to develop guidelines that request external sponsors add each site to the online CTN's "trial site details" only after receiving written site authorisation.

INTERNAL SPONSORS – Investigator-initiated / institution-sponsored

How should an institution manage and maintain quality over investigator-initiated CTN submissions?

The TGA Business Services website (and thus, the online CTN) allows for one "administrator" per organisation. Per the TGA Business Services (TBS) Terms and Conditions, the TBS Administrator is responsible for the establishment and management of all users for the specific organisation that the Administrator represents, and must ensure that all users within the organisation are aware of, and comply with, the terms and conditions for use of their access to TBS. Each account is registered to a legal entity, and it is therefore up to each organisation to determine how to administer its own account.

There is currently no mechanism for organisations to confirm with the TGA the number of accounts that have been registered as part of the organisation. However, the account administrator can view all notifications under its account.

The administrator is responsible for assigning user roles to others within the organisation, including roles for "drafter" (who can draft but not submit a CTN), "submitter" and "financial." Administrators cannot assign the Administrator role to another contact within their organisation (see footnote under the roles table here). The administrator can also check an authorisation box for each contact in the system, which controls whether the contact can speak to the TGA on the organisation's behalf. Specifics of each role are outlined here under "Roles: what each user can do."

OHMR recommends institutions select an administrator who is independent from - and does not also act as - a study investigator. For investigator-initiated (i.e. institution-sponsored) trials, an institution may choose to establish a central system for the tracking and administration of user roles within the organisation. While this would be a site decision (as each site has different available resourcing), this may include a mechanism to control the number of "submitters" assigned to each network or speciality team (e.g. one submitter per team), and guidance on data entry quality and consistency, and privacy. Institutions should remind investigators that no one within the organisation may establish an online account separate from the primary account administrator.

For single-site investigator-initiated studies, institutions may choose to establish local policies that require documented receipt of HREC and site specific approval before the online CTN can be submitted. As above, OHMR recommends that the HREC Approval letter and the Site Authorisation letter be used to indicate the respective forms of approval.

For multi-site investigator-initiated studies, sponsoring institutions may choose to establish local policies that require receipt of a copy of the HREC approval letter and the Site Authorisation letter for each site, before each site can be included under the online CTN's "trial site details". Similar to the paper form processes, the online CTN may often initially include one site under "trial site details," which will be updated as documented approval for each new site is received.

While Institutions do not need to request a copy of the TGA acknowledgement of receipt of a CTN,

(acknowledgement has never been a requirement for a study to begin), it is still recommended. Please note that the TGA may phase out the provision of acknowledgement communications in the future.

How is information protected if drafters and submitters can see CTN information submitted by others within their institution?

Some institutions have raised the issue that with multiple 'drafters' and 'submitters' across their institution, researchers can view the CTN application content from other researchers, which they believe may inappropriately reveal confidential Intellectual Property. OHMR recommends that when determining access and process issues locally, institutions first decide whether this is an issue of concern for them, and develop access policies accordingly. For instance, it may be worthwhile for all submissions to be handled by the research office rather than by the researchers themselves, depending on perceived burden to the office.

The Agent option: establishing multiple client ID's: Sponsors may choose to establish multiple TBS accounts (and thus, multiple client identification numbers) as separate entities, which are linked to one Agent within TBS. Under this model, 'submitters' from each separate entity would not be able to view CTNs submitted under the other entities.

As an example, the governance office at Central Hospital would like to permit multiple departments and/or researchers to submit CTNs under separate client IDs. Using the Organisation Details form, the office member selects "Agent" under "organisation role," and enters "Central Hospital" as the "Organisation Name" on page 1. Each department fills out a separate Organisational Details form, but selects "Sponsor" under "organisation role," and its department name as the "Organisation Name" (e.g. "Central Hospital – Department of Dental Surgery.") The order in which these applications are submitted does not matter.

To establish the Agent relationship, each department under Central Hospital then fills out an "Add or remove an Agent from your organisation" form, which authorises or removes an agent to undertake regulatory correspondence with the TGA.

Once processed, the Agent can view all submitted CTNs under each linked organisation once they reach the Clinical Trials Repository within the system, but cannot view draft CTNs. The individual departments cannot view each other's submissions, nor can they view any CTNs that may have been submitted under the Agent's Client ID. Under this model, the Agent, as with any other client in TBS, can allocate an administrator who is responsible for assigning user roles to others within the organisation. The Agent can also submit CTNs under its Client ID. Per the TGA, careful consideration should be given before requesting an agent/sponsor relationship.

Do sponsors need to retain copies of submitted CTNs?

Per the TGA's Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA comments, the TGA requires sponsor-specific essential documents be retained "until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor." CTN documents fall under this requirement, since "regulatory authority(ies) authorisation/ approval/ notification of protocol" is an essential document under ICH GCP section 8.

Submitted CTNs are stored in the TBS system in an area called the Clinical Trials Repository. They remain in the Repository (sponsor's view) until such time that a completion advice is lodged by the sponsor advising the TGA that the trial has been completed. At that stage, the trial will no longer appear in the sponsor's view. Therefore, it is recommended that sponsors retain copies of submitted CTNs.

How can I submit questions and feedback on the online CTN to NSW Health?

OHMR has worked closely with local and national stakeholders to determine the scope and content of this guidance document. OHMR welcomes information on stakeholder experiences with the online CTN. Please email your feedback via email to HEALTHETHICS@doh.health.nsw.gov.au.

How can I submit questions and feedback to the TGA?

The TGA welcomes feedback on the new online format. Feedback can be sent directly to the TGA at clinical.trials@tga.gov.au.