Do all services provided as part of a clinical trial require research ethics and governance review?

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Abstract

Appropriate ethical oversight underpins the conduct of all clinical trials in Australia. In addition, clinical trials require research governance approach in order to ensure that research is appropriately governed. However, such governance processes that all too often are onerous and time-consuming required when trial practices mimic usual standards of care.

DO ALL SERVICES PROVIDED AS PART OF A CLINICAL TRIAL REQUIRE RESEARCH ETHICS AND GOVERNANCE REVIEW?

It is universally accepted in Australia that the conduct of a clinical trial requires initial review by a human research ethics committee. In recent years, this review has been accompanied by an assessment, sometimes referred to as 'governance review', by each institution participating in the trial in order to obtain authorisation of the project for each trial site. In keeping with a robust research governance framework, ongoing monitoring of the project by the reviewing Human Research Ethics Committee (HREC) and by each institution is also required.

However, many hospitals, particularly specialist hospitals, or clinical practices (eg a GP practice) may provide what is, for them, a routine service to patients on referral from other institutions/practices where these patients are participants in a clinical trial that is not being conducted at the institution/practice to which the patient is referred. These services may relate to diagnosis, treatment or care of patients and may include pathology tests, imaging, radiotherapy, surgery, chemotherapy, counselling or palliative care. Non-hospital service providers such as laboratories or private clinics may also provide such services.

We are concerned that a research governance paradigm, with its extensive review and oversight requirements, is being imposed on routine (standard care) clinical services provided to research participants at the institution to which such participants have been referred.

We argue that, in circumstances in which institutional 'standard of care' clinical services are provided on referral, the service providers should not be considered 'trial sites' and, as a consequence, should not be obliged to provide or ensure ethics review for the research project. Further, if appropriate steps (described below) are taken to ensure the welfare and safety of participants and authorised access to data arising out of the provision of such services, it is not necessary for the provision of these services to be subjected to the standard site assessment or authorisation/research governance process for the conduct of a clinical trial at a participating site.

Discussion

To be considered a trial site, an institution must either provide trial-specific services in accordance with the trial protocol or provide resources specifically for the conduct of the trial, or at least one of its contracted staff (employee, consultant or independent contractor) must be involved in trial-related activity, including, potentially, making a contribution to analysis of data, publication or dissemination of outcomes from the trial.

However, we believe that not all clinical services or other contributions to a clinical trial are equivalent to the 'conduct of a clinical trial' that triggers the need for the review, assessment and monitoring by formally constituted research ethics committees or those responsible for research governance. When these services are provided such that

- the services are provided on referral from another institution (or a clinician) that is itself a trial site *and*
- the trial participants return to the trial site for any trial-specific procedures *and*
- the site to which the patient has been referred is providing what, for that site, is routine care *and*
- the provider of the services is not otherwise involved in the clinical trial,

then an alternative paradigm is appropriate.

It is our contention that, if the conditions listed above are satisfied, then the services provided are not being performed as part of a clinical trial. Hence, the provision of the services should not be subject to scrutiny,

assessment or other governance processes other than those that normally apply to the oversight of clinical care – specifically, they do not require the level of oversight that is ordinarily provided as part of a research paradigm.

The critical question is whether the service provided by a hospital, laboratory or other service provider to patients (who are also participants in a clinical trial active at a referring institution) is or is not a trial-specific procedure. A trial-specific procedure can be defined as *any procedure that is not required or not normally conducted as part of standard of care (SOC) but is included in a clinical trial protocol OR as any procedure included in a clinical trial protocol (whether or not it is standard of care) that would not be provided to a patient unless they were enrolled in the trial*. This distinction is less important when the institution providing the care is also conducting the trial; but when the service is being provided following referral to a non-participating institution, the distinction becomes critical. **We note that, with reference to the second definition of trial-specific procedure, the characterisation of a service as a trial-specific procedure or as usual care will either be in accordance with an established institutional process or determined by the research team on a case-by-case basis, with consequent implications for how the service is paid for, i.e. by an external trial sponsor or by the service provider per standard billing processes.**¹

As an example, consider a prospective, randomised, open label phase II clinical trial in which two alternative chemotherapeutic regimens (chemotherapy regimen A vs. chemotherapy regimen B) given before radiotherapy are being compared and for which the primary endpoint is progression free survival. As part of this hypothetical trial, the participants will undergo imaging, blood samples will be taken and all participants will receive radiotherapy as part of the standard of care for patients with this condition, regardless of the arm of the trial to which they are randomized.

A hospital participating in the trial (the trial site) does not have the capacity to provide the radiotherapy and routinely refers its patients to another hospital for this service. That is, referral of these patients for radiotherapy would occur whether or not the patients were participating in the clinical trial. Meanwhile, the patients in question are undergoing all investigational and other interventional procedures (i.e. chemotherapeutic treatment, imaging tests and blood samples that are specific to the trial and to which they would not otherwise be subject) at the trial site.

In this scenario, if the hospital providing the radiotherapy is not otherwise conducting the trial and is, consequently, not a participating site, then the service that it is providing on referral cannot reasonably be considered a ‘trial-specific procedure’. Accordingly, what it is providing is a clinical service that is governed by the oversight mechanisms and processes in place for the provision of clinical services at that institution. **We note that, while acceptance of this principle will have implications for the scope of the trial sponsor’s management of the conduct of the trial, this is, in principle, no different than patients continuing to receive health care from any source (such as their GP) that has no relationship to the trial.**

However, by virtue of providing services to patients participating in a clinical trial, the institution providing standard of care services on referral does have some additional responsibilities related to the clinical trial, even though it is not a participating site. These responsibilities, which arise out of its duty of care, include ensuring that

1. the second institution is aware that the services in question are being provided to patients who are participants in a clinical trial at another site

¹ It is important that costing issues are addressed early in the planning of a trial and clearly set out in any relevant agreements to avoid disputes over financial matters and to ensure that sponsors accept that the services to be provided as standard care are acceptable.

2. any adverse events that occur related to the provision of the services in question are notified to the clinical trial project team at the referring site in accordance with standard protocols, as well as being notified internally via routine clinical governance processes, and
3. the institution agrees to provide the trial site and/or trial sponsor with access to any data that is generated as part of the provision of the services in question that are not otherwise available from the referring trial site.²

Governance of clinical trials and other research has advanced considerably in recent years in Australia. Moreover, there is an increasing recognition that clinical care and research are, optimally, closely linked. Overall, these are positive developments; however, there is a clear danger of over-burdening health care institutions providing clinical services on referral if the provision of these services provided to patients who are also clinical trial participants elsewhere are subject to the necessarily rigorous oversight of clinical trials that is required by institutional, state, national and international policies and guidelines. It is our contention that a robust clinical governance framework is sufficient for oversight of these activities and that this model preserves the necessary distinction between institutional governance of clinical activities versus governance of research conducted under its auspices.

² Patients will have already consented to the provision of trial-related information to the trial sponsor, but, in this case, the results of standard treatments should also be provided. The disclosure of such information is standard practice when patients move from one institution to another for standard treatments outside of the clinical trial context.

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