Contract Research Organisations (CROs) supporting patients in clinical trials during the COVID-19 pandemic in Australia

summary

The COVID-19 pandemic will be a transformational disruption for all aspects of society, including the healthcare sector. The clinical trials sector has had to adapt quickly to ensure the successful continuation and management of clinical trials during the acute phase of the pandemic. We will equally need a rapid response as we prepare for the recovery phase and beyond.

POSITION STATEMENT

16 June 2020

This position statement was prepared with the support of the following CROs.

ARCS CRO Steering committee

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Clinical trials remain critical to bring innovative drugs, vaccines, medical devices and diagnostics and therapies to consumers and patients in Australia in a safe and regulated manner. Given the predicted impact of COVID-19 on the health system and services, CROs and others in the sector are working with doctors, research nurses and clinical trial sites to prepare for disruption of normal research activities. At all times, the safety and continuity of care of clinical trial participants is the key concern of all professionals working with patients.

The value of CROs in the clinical trial sector

The global CRO market value reached US$39 billion in 2018 and is expected to exceed US$44 billion by 2021, as patent expiry, proliferation of generic medications, technological innovation and big data influence product development leading to greater outsourcing of work to CROs.

Contract Research Organisations are essential to the pharma, biotech and MedTech industries. They support clients efforts to test, refine and market the latest pharmaceuticals and medical devices.

Australian CROs

In Australia, CROs play a critical role in delivering clinical trials for both sponsored and investigator led trials. There are currently 20 companies operating in Australia offering resources, capability and capacity to deliver trials from First-In-Human (Phase 1) through to post-marketing surveillance (Phase 4). CROs are committed to the delivery of clinical research and to ensure that the clinical trials already underway are managed as well as can be during the pandemic. CROs are working closely with clinical trial centre staff to understand what additional support can be provided to overcome the challenges that are presenting due to COVID-19 disruptions.

This statement was prepared in recognition of the challenges the health system faces. We acknowledge the physicians, nurses, allied healthcare workers and scientists for their efforts during the course of this pandemic.

It also acknowledges the position statements released by the CTPRG[1] and peak body R&DTF[2] as well as specific state-based statements.

It also acknowledges and builds on these statements to highlight and detail elements that are essential as we work with stakeholders towards a COVID-19 recovery phase and ensure that the positive changes we have seen happen during the pandemic are captured through guidances, standards, policies and potentially legislation.

Whilst we are all keen to see a post-COVID-19 world, we feel that until a vaccine or other treatment is developed, we will continue to work in a highly contained environment that will necessitate the continuation of many lockdown measures.

One of the major (and lasting) impacts of the COVID-19 pandemic is hearing from clinicians of the number of patients who have not been able to access lifesaving therapy via new clinical trials.

Now aware of the shortcomings and potential solutions, we have a moral obligation to adapt our processes to futureproof the local research ecosystem to disruptions, which could have a major impact on the safety and wellbeing of clinical trial participants.

Therefore, one of the primary aims of this paper is to outline adaptions to date across our sector, lessons learnt and best practices adopted during COVID-19 with the aim of embedding these as "business as usual" in a post-pandemic research landscape for the broader clinical trial sector.

The three key elements of this statement are:

1

Australia remains open for establishing new clinical trials and supporting ongoing clinical trials, which save lives, improves the health and quality of life of participants. Together with technology shift, we need cultural shift. This means working with and educating our workforces to embrace change and reimagine how we do healthcare.

Global CROs and clinical trial sponsors are looking to Australia and New Zealand as we manage and control the spread of COVID-19, while Europe and the US continues to struggle with high rates of infections. It highlights the unique position Australia is in to capture new business and build the sector. To enable this, we need to ensure a risk-based assessment of all clinical trial activities continues which ensures the safety of participants[3], site, sponsor and CRO staff involved in trials is balanced against study and data integrity.

To enable these health and economic opportunities, we are calling for a national approach to identify clinical trial sites and site status (as defined in Appendix A) which assists all stakeholders attract and implement clinical trials in Australia in a timely and cost-effective manner for the wellbeing all participants.

2

Embedding key virtual processes and decentralised trials is essential to improve the conduct of clinical trials in Australia.

To ensure continuity of clinical trials through the pandemic, we have seen the many processes that have had to be rapidly modified and implemented to ensure continued access of clinical trials for participants. The adoption of some of these practices had started before COVID-19 but we have seen increased acceptability by all stakeholders which we would like to see continue.

These changes need to be nationalised and standardised. These include:

A national approach to the adoption of a patient centric decentralised process

COVID-19 has seen the necessary adoption of processes which put the participant at the centre of clinical trial operational decision making with the adoption of activities such as the delivery of trial investigational product direct to patients, and the use of local labs and imaging centres.

We are calling for the development of national standards which facilitates embedding patient centric decentralised research practices in Australia.

eSignatures

Collecting wet ink signatures from the multiple signatories required for contracts has been a significant administrative burden delaying study start-up. With COVID-19 we have seen a marked increase in willingness to accept eSignatures resulting in improved efficiency and positive impact on start-up times for all research stakeholders. This ultimately facilitates rapid access to clinical trials for patients.

We are calling for the development of national standards, independent of software solutions and based on international regulations (21 CFR part 11), which, at a country level, harmonises electronic signatures.

Telehealth

COVID-19 has changed the public understanding and acceptability of telehealth in Australia. Telehealth is an important part of ensuring potential participants have access to clinical trials regardless of their location.

We are calling for the development of national standard operating procedures to:

(1) Ensure rapid and seamless deployment of clinical trials to remote patients

(2) Expand the current pilot program across every state and territory with clear timelines and goals

(3) Establish an educational program to support the adoption and imbedding of telehealth with research sites which have not yet adopted the technology

(4) Establish national standards that can be adopted across the jurisdictions.

2 Continued

eConsent

COVID-19 has seen the necessary adoption of different elements of the informed consent process such as electronic consent (eConsent) to ensure that participants are fully informed as defined in local regulation and ICH-GCP before enrolling in clinical trials while not exposing them to any additional risks. eConsent is defined as:

> "the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent."[4]

Use of Electronic Informed Consent Questions and Answers Guidance for Institutional Review Boards, Investigators, and Sponsors (December 2016). Jointly prepared by the Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA).

We are calling for the development of national standards, based on international regulations such as the FDAs[5], which accepts and harmonises the use of eConsent across jurisdictions in Australia. FDA's requirements for electronic records/electronic signatures, informed consent, and IRBs (in Australia, an ethics committee) are set forth in FDA 21 CFR parts 11, 50, and 56, respectively.

Remote Monitoring

Data validity and the integrity of research results ensure trial outcomes are valid. This will be particularly important as we promote remote monitoring to patients. Underpinning remote monitoring of clinical trials is electronic and remote access to electronic medical records (EMR). We acknowledge that the broader community is still cautious on all matters related to health data. For this paper, remote monitoring, remote source data monitoring and remote data verification are defined as:

Remote Monitoring - Remote Monitoring is the term used to describe site management and oversight activities that are implemented to manage risk on clinical trials. Remote monitoring may include review of electronic case report forms (eCRF) data and study related documentation but does not include any data verification of source documents or copies of source documents.

Remote Source Data Monitoring (rSDM) - Remote Source Data Monitoring is the review of source data (medical records and source notes) via remote access to a secure and restricted EMR or an eSource platform. Information in these systems are typically in an identifiable format but may be de-identified.

Remote Data Verification (rDV) - Remote Data Verification is the review of specific certified copies of de-identified records. These can be copies of reports/records and copies of source data that are scanned/faxed/emailed securely for review.

We are calling for a national approach underpinned by legislation to assure future accessibility as the Australian community attitude changes on this matter. We further call for incentives for states to commit to a national approach to conducting clinical trials and harmonise activities underpinned by direct access to EMR with the appropriate governance and legislative considerations including:

a. *FDA 21 CFR part 11 compliance*
b. *Controls relating to access and account management*
c. *Extent of source data available or excluded by the rSDM solution*
d. *IT security of any application used to access the EMR/eSource*
e. *Current and future ethical considerations, and national informed consent wording.*

We acknowledge the more conservative position presented by EMA[6] in relation to remote monitoring.

3

Eliminating redundancy to improve our start up times and our competitiveness internationally.

COVID-19 has demonstrated that research ethics and governance can be streamlined and made into an efficient process without compromising its role in oversight of research involving humans. The adoption of virtual ethics meetings has unlocked efficiencies (and with investigators attending virtually have reduced the number of cycles). COVID-19 necessitated a risk-based approach to be front and centre of research governance activities. The reduction in volume, the triaging of research and the move to electronic documents and signatures has been central to these improvements. Improved start-up times for trials will ensure that, irrespective of times of crisis, we can be more responsive to the needs of patients and their access to clinical trials.

We are calling for

a. *Putting the patient at the centre of start-up considerations by prioritising trials involving lifesaving therapies and those addressing unmet medical need and critical illness over other research projects.*

b. *The implementation of a national 'front door' digital platform that harmonises information and identification of active sites (specifications to be finalised via consultation with industry).*

c. *A distributed ethics model[7] that provides guiding principles to committees and virtual meetings for rapid assessment, particularly for low and negligible risk studies.*

d. *The prioritisation of research dealing with lifesaving treatments and for patient populations where no other treatment options are available.*

e. *A 'call centre' or 'a curated record of FAQs', such as the ACTA blog, for problem solving with people who can assist researchers and governance teams with fast decisions.*

f. *The establishment of centres of excellence which support investigational sites during the start-up phase by providing guidance and tips utilising the experience and expertise of centre personnel.*

This position paper has been developed by ARCS Australia[8] as an outcome from the 2020 ARCS virtual CRO forum (May 2020).

ARCS Australia and the participating CROs acknowledge the incredible work being undertaken by the hospitals, clinical sites and the federal and state/territory health departments as we all navigate this pandemic.

References

1. Clinical Trial Project Reference Group https://www.health.gov.au/
2. Research & Development Taskforce – a committee of the industry Peak bodies, MA, MTAA and AusBiotech
3. https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods#block-views-block-file-attachments-content-block-1
4. Use of Electronic Informed Consent Questions and Answers Guidance for Institutional Review Boards, Investigators, and Sponsors (December 2016). Jointly prepared by the Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA).
5. FDA's requirements for electronic records/electronic signatures, informed consent, and IRBs are set forth in FDA 21 CFR parts 11, 50, and 56, respectively.
6. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
7. Concept of decentralised access to committee members to supplement committees during COVID-19
8. ARCS Australia is a national, membership-based organisation focused on the development and growth of the healthcare sector. ARCS and its members are dedicated to improving the quality of life of healthcare consumers and adding value to the healthcare sector, through the provision of education, career pathways, professional development and advocacy.

Appendix A:

The follow criteria collected at a national level would improve the ability of all stakeholders to attract clinical research to Australia and to proactively minimise the effects of future disruptions.

Site status update (a national approach):

- Business as usual
- Recruitment on hold
- Study visit hold (for non-essential / non-treatment visits)
- Site open (patients seen at a secondary location(s))
- Site open (for selected studies)
- Site closed to all non-essential studies
- Site closed to new feasibilities
- Site closed to onsite monitoring
- HREC/RGO closed to non-essential studies

Is the clinical trial site set up to enable remote monitoring? If yes, does this include (tick all that apply).

- Remote SDV?
- Do you have the staff resource to supply redacted source notes?
- Does your HREC require participant consent for redacted source notes to be provided?
- Do you require additional payment to supply redacted source notes?
- Do you have remote access to EMR*? (Yes, No, Other. If other, please explain)
- Do you have remote access to eSource*? (Yes, No, Other. If other, please explain)
- Do you have capabilities for telehealth? (Yes, No, Other. If other, please explain)
- Do you have SOPs in place to allow remote monitoring? Other. If other, please explain)
- Do you have strategies to Direct to Patient IP supply? Other. If other, please explain)

If No

- Are you assessing the feasibility of implementing remote monitoring capabilities at your site within the next 12 months?
- Are you part of a monitoring hub (centrally secure location)?

** FDA21 CRF part 11 compliance*