# A Study to compare two approaches of remote monitoring used for BALANCE trial – Source data verification via uploading of documents vs source data verification via live monitoring

Protocol Version 1

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**Aim**

The primary aim of the study is to test and compare the two approaches of remote monitoring: Source data verification via uploading of documents and source data verification via live monitoring through a platform such as zoom

**Background and significance–**

Clinical trial monitoring is a crucial part of trial conduct, improving the safety of the participants, the quality of the data and the trial integrity. Clinical trial monitoring is conducted by monitors, quality assurance teams and by trial managers (Love et al, 2020). The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) gives a definition of the purpose of clinical trial monitoring

The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s)."

Though ICH GCP has used this underlying definition of the purpose of monitoring since 1996 (ICH guidelines for good clinical practice, 2018), it is not written in accessible language and does not contain any explicit detailed guidance on monitoring activities (Houston et al, 2021). This has led to wide variation in practices and there are different approaches of monitoring are being used.

Australian monitoring recommendations are defined by the NHMRC Guidance documents 'Safety monitoring and reporting in clinical trials involving therapeutic goods, Nov 2016' and the 'Risk-based management and monitoring of Clinical Trials involving therapeutic goods, 2018'. The later document provides key guidance for non-commercially sponsored trials such as BALANCE.

Over the last decade, there has been international recognition that a more flexible and tailored approach to managing clinical trials should be encouraged, because current practices do not seem to be achieving their desired goals, namely, creating an environment that facilitates, cost effective, high quality clinical trials. The Integrated Addendum to ICH E6 R1: Guidelines for Good Clinical Practice (ICH E6 R2) [1] has been amended to embed a risk-based approach to Good Clinical Practice (GCP). This approach is also endorsed by regulatory authorities including the European Medicines Agency and the US Food and Drugs Administration (FDA) as well as by NHMRC in Australia.

The BALANCE trial is a multicentre, randomized trial of shorter duration (7 days) versus longer duration (14 days) antibiotic treatment for patients with bloodstream infections admitted to hospital (in either ICU or Non-ICU wards). The BALANCE trial involves the use of only antimicrobials entered into the ARTG (registered for use in Australia). Based on this, BALANCE is

classified as a risk Category type B trial (risk associated with the modified use of an existing product). BALANCE trial monitors the sites using central monitoring already. Central monitoring involves the review of centralised data, for example, by trial oversight committees or data management personnel. This includes the central review of data from sites (e.g., a review of the completeness of the Case Report Form).

The COVID-19 pandemic affected how clinical trials are managed, both within existing portfolios and for the rapidly developed COVID-19 trials. Sponsors or delegated organisations responsible for monitoring trials needed to consider and implement alternative ways of working due to the infection risk necessitating restricted movement of staff and public, reduced clinical staff resource as research staff moved to clinical areas, and amended working arrangements for sponsor and sponsor delegates as staff moved to working from home. (Love et all, 2021). This led to increase in remote monitoring for clinical trials. As per The NHMRC guidelines (guidance on clinical trials for institutions during COVID-19 – for HRECs, researchers and sponsors), remote monitoring visits are encouraged as the first option in all cases and sponsors and institutions should ensure that these are facilitated, taking into account the need to avoid undue burden on hospital or institutional resources.

Based on the trial risk categorisation of BALANCE trial, Australian national guidelines support the use of remote monitoring for this type of trial. The term remote monitoring describes monitoring activities that were previously conducted at the trial site by the trial monitor, but can now be conducted off-site (e.g., the review of documents sent by e-mail) (NHMRC guidelines on Risk-based management and monitoring of Clinical Trials involving therapeutic goods, 2018')

Remote monitoring may include documents such as informed consent forms (ICFs) being sent to the central office to enable a number of checks to be performed with data protection issues addressed, site self-completed monitoring checklists or telephone/video monitoring calls. A key component of the monitoring is Source Data Verification (SDV), where the primary document is reviewed by a monitor for completeness and accuracy. There are three key approaches used for SDV. a) 'Document up-load' SDV where a site shares requested documents through fax, email, upload into cloud-based file share system for review by the monitor at a later time b) 'Live video' SDV where the study monitor reviews and confirms source data in real-time over a video-link with the study site c) sites may facilitate a monitor's direct access to their electronic medical record (EMR) allowing the monitor to directly locate and review source data.

However, there isn't sufficient literature to suggest the benefits of different approaches and also when and if one method should be preferred over the other. In this study, we aim to compare the two most commonly used approaches to SDV (document up-load and live video) and evaluate the effectiveness of both approaches.

**Specific Aims:**

**Aim: To compare two methods of remote monitoring: uploading of documents vs live online monitoring.**

**Objectives:**

**To compare between the two methods:**

1. To evaluate the time taken by the monitor and by the site staff to complete monitoring using two approaches

2. To compare the acceptability and user preference of two approaches
3. To assess the quality of monitoring using the two approaches

**Methods:**

**Randomised trial embedded within ongoing practice of study monitoring for BALANCE**

**Design:** This is an embedded pragmatic randomised trial.
**Inclusion criteria:** all sites participating in BALALNCE trial in Australia (n=18) will be invited to participate in the study.
**Exclusion Criteria:** Nil. Sites not willing to participate in the study will be excluded.
**Study Procedure:** Sites will be approached to participate in this study. Sites that agree will be randomised 1:1 to SDV verification by either document upload or live video. Sites will be randomised in permuted blocks of 4 using an excel spreadsheet random number function. The details of the two methods of SDV are as specified and described in the main BALANCE trial documentation (reference).

**Data collection:**

Extraction of quantitative data from approved study monitoring documentation:

For consistency across all participating sites and comparison, pre-designed site monitoring template will be used to record the data points during monitoring (Appendix). In addition, following data will be collected:

Time taken (minutes) by the study site to complete each of the SDV components in the study monitoring is recorded in the approved SDV workflow for the study. This will be extracted from the approved worksheet.

Number of source documents/platforms accessed to complete SDV components is recorded in the approved SDV workflow. This will be extracted.

Study Monitor time: The study monitor will record the time (minutes) it takes to verify each component of source data for the sites.

Quality: Will be extracted from the information collected as part of monitoring

Preference and usability survey: Site trial staff participating in the SDV will be surveyed. Please see appendix.

**Consent:**

Direct informed consent is not being requested for this non-clinical trial. Sites will be informed about the study as part of information on study monitoring at their site. Sites will have the option to opt out, if they do not wish to participate. Sites that are not willing to participate in this study will have the option to choose one of the approaches for monitoring at their site.

Completion of the preference and usability survey is optional.

**Data storage and Statistical Analysis:**

Data will be recorded in a password protected file available only to the investigators. No identifying data about the site staff who completed the monitor or details of trial participants monitored will be retained. Any publications or presentations of this study will present de-identified and aggregated data that will not allow the identification of individual study sites.

Descriptive statistics for ordinal and nominal variables will be presented in figures. Normal distribution of continuous data will be assessed using the Shapiro-Wilk test. Continuous variables will be expressed as mean ± SD or median (IQR). Comparisons will be made using t-test and ANOVA for repeated-measures or Wilcoxon rank-signed test and Kruskall-Wallis according to the underlying distribution for continuous data and Chi-square of Fisher's exact test for categorical data.

**References:**


1. Love SB, Yorke-Edwards V, Lensen S, et al. Monitoring in practice - how are UK academic clinical trials monitored? A survey. Trials. 2020; 21:59 https://doi.org/10.1186/s13063-019-3619-6
2. ICH. International Conference on Harmonisation of technical requirements for pharmaceuticals for human use (ICH). Guideline for good clinical practice E6(R2) 2018. 1996. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf. Accessed 14 July 2020.
3. Houston L, Martin A, Yu P, et al. Time-consuming and expensive data quality monitoring procedures persist in clinical trials: a national survey. Contemp Clin Trials. 2021; 103:106290. https://doi.org/10.1016/j.cct.2021.106290.
4. Food and Administration: Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring (Aug 2013)
5. European Medicines Agency: Reflection paper on risk-based quality management in clinical trials (Nov 2013).
6. Consultation Document: Risk proportionate approaches in clinical trials: Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use
7. NHMRC guidelines on Risk-based management and monitoring of Clinical Trials involving therapeutic goods2018 https://www.australianclinicaltrials.gov.au/sites/default/files/content/For%20researchers/Risk-Based%20Management%20and%20Monitoring%20of%20Clinical%20Trials.pdf
8. COVID-19: Guidance on clinical trials for institutions, HRECs, researchers and sponsors
9. https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05225-5


**Appendix 1. Survey for research staff participating in monitoring**

**Question 1.** What kind of remote monitoring did your site participate in?

a.) SDV via Uploading of documents
b.) SDV via screen share

**Question 2:** What was the total number of participants monitored at your site?

a.) Select number from drop-down

**Question 3.** How many years have you worked in clinical research?

a.) 0-1Years

b.) 2-5 years

c.) 6-9 years

d.) 10+ years

**Question 5.** Have you participated in clinical trial study monitoring activities before?

a.) Yes
b.) No

**Question 6.** If you answered 'yes' to question 5, what kind of monitoring have you participated in before?

a.) On site face to face monitoring – Yes/No
b.) Remote monitoring with SDV upload – Yes/NO
c.) Remote monitoring via live online SDV verification – Yes/No

**Question 7. (If answered Y to a), b) or c) in Q6)** Do you prefer this method of monitoring as compared to the monitoring approach that you have participated in the past? Please select the most appropriate answer from the following:

a.) I prefer this method of monitoring than on site face to face monitoring - Yes/No
b.) I prefer this method of monitoring than remote monitoring involving uploading of SDV – Yes/No/NA
c.) I prefer this method of monitoring than remote monitoring via live online SDV verification – Yes/No/NA
d.) I have no preference

**Question 8.** Does your hospital have well established electronic medical record?

a.) Yes
b.) No
c.) Mix of paper and electronic medical records

**Question 9.** The monitoring method I participated in was an efficient use of my time to complete this task.

Strongly disagree 1 2 3 4 5 strongly agree

**Question 9.** I would recommend participating in this method of monitoring in the future?

Strongly disagree 1 2 3 4 5 strongly agree

**Question 10.** I think the monitoring method adequately protected patient privacy and confidentiality?

Strongly disagree 1 2 3 4 5 strongly agree

**Question 11.** I felt this method of monitoring was accurate and valid in SDV.

Strongly disagree 1 2 3 4 5 strongly agree

**Question 12.** Any other comments or suggestions that you may have on remote study monitoring?

**Appendix 2: Survey for monitoring staff**

Type of monitoring approach used:

Site Number:

Question 1. Number of issues/protocol deviations that needed correction on the CRF

a.) <5
b.) 5-10
c.) 10-20