

Monitoring Advances Including Consent; Learning from COVID-19 Trials and Other Trials Running in UKCRC Registered Clinical Trials Units During the COVID-19 Pandemic

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Abstract

Background

The COVID-19 pandemic has 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 have needed to consider and implement alternative ways of working due to the national 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.

Organisations have often worked in isolation to fast track mitigations required for the conduct of clinical trials during the pandemic; this paper describes many of the learnings from a group of monitoring leads based in UKCRC Clinical Trials Unit (CTUs) within the UK.

Methods

The UKCRC Monitoring Task and Finish Group comprising monitoring leads from 9 CTUs, met repeatedly to identify how COVID-19 had affected clinical trial monitoring. Informed consent is included as a specific issue within this paper, as review of completed consent documentation is often required within trial monitoring plans (TMPs). Monitoring is defined as involving on-site monitoring, central monitoring or/and remote monitoring.

Results

Monitoring, required to protect the safety of the patients, the integrity of the trial and ensure the protocol is followed, is often best done by a combination of central, remote and on-site monitoring. However, if on-site monitoring is not possible, workable solutions can be found using only central or central and remote monitoring. eConsent, consent by a third person, or via remote means is plausible. Minimising datasets to the critical data reduces workload for sites and CTU staff. Home working caused by COVID-19 has made electronic trial master files (TMF's) more inviting. Allowing sites to book and attend protocol training at a time convenient to them has been successful and worth pursuing for trials with many sites in the future.

Conclusions

The arrival of COVID-19 in the UK has forced consideration of and changes to how clinical trials are conducted in relation to monitoring. Some developed practices will be useful in other pandemics and others should be incorporated into regular use.

Background

Clinical trialists monitor trial data in order to protect the rights and well-being of participants, to ensure that the trial data are accurate, complete, and verifiable, and to confirm that the trial is being run in compliance

with the currently approved protocol, with the principles of good clinical practice (GCP), and with the relevant regulatory requirements (1).

The Food and Drug Administration (FDA) (2), European Medicines Agency (EMA) (3) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP E6(R2) (1) promote risk-based monitoring. In risk-based monitoring, the monitoring activities are directed at preventing or mitigating important and likely risks to data quality, to processes critical to human subject protection and to trial integrity. Rather than monitoring routinely throughout the trial, the monitoring is directed at pre-defined risks to the trial, and to risks which become apparent during the active phase. The Medicines and Healthcare Products Regulatory Agency (MHRA) and others have published guidance on risk-proportionate approaches (4).

In March 2020, COVID-19 intervened in the trial arena. Trialists in the UK, like elsewhere, had to adapt to and define a different way of working as even those academic sponsors who had pandemic/epidemic SOPs had not used them in practice. COVID-19 trials were designed and opened at a fast rate with RECOVERY-RS (ISRCTN16912075) (5) recruiting the first patient just 10 days after draft protocol. As part of this, those leading monitoring within clinical trial units adapted as well. Often staff not directly involved in patient care were discouraged from accessing hospitals. This was due to the requirement for a reduction in footfall within hospital settings for safety reasons to restrict the spread of COVID-19 and also because research staff at hospitals were being resourced into different areas to ensure clinical care was prioritised. This made routine on-site monitoring impossible. For COVID-19 trials, the use of paper-based documents became a problem and hospitals had a variety of requirements for ensuring cross contamination from paper was mitigated for, such as not allowing paper out of COVID-19 areas or delaying movement of paper out of COVID-19 areas for a specific number of days. Within the context of clinical trials this affected informed consent as well as medical documentation. Monitoring of trials therefore needed to adapt. In this paper we report the learnings of a group of monitoring leads in the UK. Some are specific to COVID-19 trials, or to trials of similar infection/mode of transmission, some are also suitable to non-COVID-19 trials operating during a pandemic and some are ways of working that could be used as routine post the COVID-19 pandemic.

Methods

The UKCRC Monitoring Task and Finish Group comprising monitoring leads from 9 CTUs, met repeatedly during April to June 2020 to identify how COVID-19 had affected clinical trial monitoring. This paper reports changes that were identified across more than one trial and more than one trials unit. Informed consent is included as a specific issue within this paper, as review of completed consent documentation is often required within trial monitoring plans (TMPs).

Definitions

The term 'monitoring' is used for the activity of overseeing the progress of a clinical trial and of ensuring that it is conducted, recorded and reported in accordance with the protocol, written procedures, GCP and

applicable regulatory requirements (6). The type of monitoring conducted by CTUs for a particular trial is determined by a risk assessment (7) and summarised in a trial monitoring plan.

On-site monitoring is monitoring performed at the investigator sites at which the clinical trial is being conducted, via a physical visit by individuals from the sponsor and/or its representatives. It requires access to the medical records of trial participants for the purposes of source data verification/review, to confirm accuracy of data transcription reported on the case report form (CRF), to confirm accurate reporting of all relevant clinical information (e.g. adverse events, concomitant meds), to confirm compliance with the protocol and the principles of GCP and to verify the existence of participants. On-site monitoring would also usually include site file review, verifying investigational medicinal products (receipt, storage, dispensing, accountability and destruction), review of facilities and equipment and training of site staff. On-site monitoring may be pre-planned (routine) or may occur when an issue is found at a site by central or remote monitoring (triggered).

Centralised monitoring is monitoring performed in a location away from the investigator site, and often at clinical trial unit / sponsor offices. It involves an evaluation of accumulating data (or lack thereof), performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, statisticians, trial managers, data scientists). The aim is to mitigate specific trial risks defined in the risk assessment document which is completed before recruitment and continually reviewed during the lifetime of the trial. Data by site are examined to identify trends, outliers, anomalies, protocol deviations and inconsistencies. Concerns raised by members of the sponsor/ctu trial team discovered during their contact with the site is also taken into consideration. Centralised monitoring may be the only monitoring, or it may lead to an on-site monitoring visit. Centralised monitoring complements and reduces the extent and/or frequency of on-site monitoring and helps distinguish between reliable data and potentially unreliable data ((1) Sect. 5.18.3). Centralised monitoring does not require trial site staff input but it may lead to requesting information from a trial site or an on-site visit.

Remote monitoring is remote evaluation performed by individuals from the sponsor or its representatives (e.g. monitors and other CTU staff) at a location remote from the trial site. It may include informed consent forms (ICFs) being sent to the central office to enable a number of checks to be performed with appropriate patient consent and data protection issues addressed, accountability logs collection, site self-completed monitoring checklists or telephone/video monitoring calls. In some instances, remote source data review (SDR) and verification (SDV) may be considered but this is dependent on sponsor procedures, site procedures and site capacity. Remote SDV/SDR may be performed by the trial site providing pseudonymised source data to the monitor, the monitor having direct access to the trial participant's electronic medical records or using a video conferencing approach. Remote monitoring requires input from the trial site.

Results

Consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is usually documented by means of a written, dual signed (patient and person taking informed consent) and dated informed consent form. In an infectious disease setting, the patient may have capacity to consent but there are practical limitations to the provision of the written evidence of this. For example, a hard copy of the patient information sheet and consent form can enter the ward, but cannot leave the ward once signed, due to the risk of infection transmission on paper documents. Various solutions have been considered and incorporated in trials investigating treatments for COVID-19 as discussed in Table 1. There are well-used options of entering adults lacking capacity to consent (8) and minors (9) onto a clinical trial without consent.

Table 1
Examples of different ways of taking consent used in COVID-19 trials

Type of consent	Comment	Pros	Cons
How consent is taken			
E-consent face-to-face	There is validated software, often linked to data management capture tools, available that can be downloaded onto a tablet for patients to provide electronic consent. Generic electronic signature products can also be used.	<p>Informed consent can be enhanced with various features e.g. video information, call out boxes, pictures, consent flags (dependent on the software solution).</p> <p>A central record can be maintained by those who require it e.g. sponsor or CTU.</p> <p>Sites have access to electronic record of the informed consent form (ICF).</p> <p>Sites can clean electronic devices between use.</p> <p>Solves the problem of moving paper within infectious areas (red zones).</p>	<p>The software has cost implications for sponsors.</p> <p>The availability of electronic devices in hospitals is limited or incurs a cost for sites or sponsor to purchase. Storage and charging need to be arranged.</p> <p>The local team may not be familiar with the software.</p> <p>Those monitoring will also need to be trained on this method/software.</p>

¹ In Scotland the 'guardian or welfare attorney' is first preference, prior to nearest relative.

Legend: 'electronic methods for seeking informed consent' and 'eConsent' refer to the use of any electronic media to convey information and to see and/ or document consent via an electronic device

Type of consent	Comment	Pros	Cons
		<p>The approach is supported by the MHRA and HRA (17).</p> <p>Some evidence that eConsent improves recruitment (18).</p>	
E-consent conducted by video call	<p>Interested participants are directed to a trial website, which outlines the study and provides the PIS. The interested participant goes through simple screening questions and those that pass are asked to provide contact details. The CTU receives the details and liaises with a clinician to call the patient. If eligible, a video call is set up with the clinician, where the PIS is discussed in full, eligibility is taken and consent is provided by the patient and clinician. On verification of consent, an email is sent to the participant which holds a link to their consent form. The clinician and CTU can access the consent form via the secure website.</p>	<p>Trial consent can be taken anywhere and the patient does not need to be co-located with the clinician.</p> <p>Site staff burden is reduced as the trial has a central group of clinicians to liaise with patients and take consent.</p> <p>Patients are not required to leave their homes during a pandemic so virus transmission risk reduced.</p> <p>Copies of the consent form are provided by email link to patients, as a record of patient consent.</p>	<p>Patients may not be familiar or comfortable with sending contact details via the trial website.</p> <p>Patients may not be familiar with video calls. Where patients do not have access to the required technology, back up measures should be considered so that they are not excluded from the research for this reason.</p> <p>Additional training requirements to conventional consent.</p> <p>Physical examinations are not possible.</p> <p>High risk trials are likely to be unsuitable, due to the virtual nature of the trial or additional steps to confirm eligibility via patient records need to be implemented.</p> <p>Need a process in place to verify the participant is who they say they are – photo ID for example</p>
<p>¹ In Scotland the 'guardian or welfare attorney' is first preference, prior to nearest relative.</p>			
<p>Legend: 'electronic methods for seeking informed consent' and 'eConsent' refer to the use of any electronic media to convey information and to see and/ or document consent via an electronic device</p>			

Type of consent	Comment	Pros	Cons
		Evidence of consent is available to sponsor/CTU by electronic means via a secure website.	
Photo of written consent	Patients are provided with paper copies of the written informed consent documents on the ward. Patients/Investigators sign and date consent and a photo or scan is taken of signed documents.	<p>There are minimal cost implications, unless hospital equipment needs to be purchased.</p> <p>Provision of consent is in line with usual process which local team are familiar with.</p> <p>Solves the problem of moving paper within infectious areas as the paper version can be processed or destroyed (and documented) in accordance with local policies.</p>	<p>Data Protection considerations must be considered. E.g. :</p> <ul style="list-style-type: none"> • Sites need to be compliant with their data protection policies/GDPR/SOPs, which does include photography. <p>Emailing identifiable images to central office may need advance consideration of data protection issues, secure transfer and site training.</p> <p>Sites need access to devices to be able to take photographs.</p> <p>Risk that signatures are not legible/visible in photos/scans, there is a risk that the photo is lost or deleted in error resulting in a loss of evidence of consent.</p>
Who takes the consent			

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Type of consent	Comment	Pros	Cons
Witness (11)	A witness could be present at the time the patient gives oral consent. The witness then provides written proof of the witnessing of oral consent in a non-infected area.	There are no cost implications, a paper copy of the written informed consent document is maintained and available for monitoring purposes.	Reliant on the availability of a witness at the time of consent.
Personal Legal Representative (PerLR)	<p>The use of personal legal representatives is a well established method of consent for use in certain situations. Some COVID-19 trials have made use of this due to patients requiring mechanical ventilation.</p> <p>A relative or close friend is approached, either in person or via telephone, provided with the relevant information sheets and asked if they feel the participant would consent to being included in the research. If they feel the participant would be happy to take part then a personal legal representative consent form is completed. In the context of COVID-19, these conversations should take place outside the infection area (red zone).</p> <p>If the participant regains capacity to consent at a later date they are provided with the relevant information sheets and are asked to complete the consent forms indicating that they are happy for data to be used/to continue in the trial.</p>	<p>No cost implications. Paper copies of written informed consent are available for monitoring purposes.</p> <p>Preferential even when the relative or close friend was on the phone and the clinician documents their consent and the clinician signs the consent form.¹</p>	<p>May be restricted to use only with patients who lack capacity to consent due to the severity of their illness.</p> <p>Family may be unsure of what the participant's wishes would be and may be reluctant to provide consent on their behalf.</p>

¹ In Scotland the 'guardian or welfare attorney' is first preference, prior to nearest relative.

Legend: 'electronic methods for seeking informed consent' and 'eConsent' refer to the use of any electronic media to convey information and to see and/ or document consent via an electronic device

Type of consent	Comment	Pros	Cons
Professional Legal Representative (ProfLR)	<p>For patients who are critically ill and are unable to provide consent and there is either no-one suitable by virtue of their relationship to the patient or a suitable person does not wish to or is unavailable to act as the legal representative, a professional legal representative (ProfLR) may be approached. This is a medical professional caring for the patient who is unconnected to the trial. If they have no medical or ethical objections to the participant taking part then a ProfLR consent form is completed. Again in the context of COVID-19 research, all paperwork should be completed and stored outside the infection area (red zone).</p> <p>If the patient regains capacity to consent, they will be asked to complete consent to continue as detailed above.</p>	No cost implications. Paper copies of written informed consent are available for monitoring purposes.	Restricted to use only with patients who lack capacity to consent due to the severity of their illness.
<p>¹ In Scotland the 'guardian or welfare attorney' is first preference, prior to nearest relative.</p>			
<p>Legend: 'electronic methods for seeking informed consent' and 'eConsent' refer to the use of any electronic media to convey information and to see and/ or document consent via an electronic device</p>			

Please could Table 1 [go here](#) During the development of COVID-19 trials, several CTUs utilised early and ongoing communication with the HRA to ensure planning of the consent process was optimal and realistic (due to limited resource at sites and various challenges associated with COVID-19 'red zones', conscious / unconscious patients, restricted (no) face to face contact with relatives).

Some COVID-19 trial designs (platform trials including more than one primary aim) were innovative in that they required consideration of several options for taking consent (Table 1). This was discussed with the HRA.

Monitoring without on-site visit option

In the setting of a global pandemic access to trial sites for non-essential staff is likely to be restricted and therefore on-site visits need to be mitigated. In the UK COVID-19 pandemic, the HRA advised trials to consider what monitoring was required immediately as opposed to what could be delayed. As long as it did not add to a site's burden, the HRA allowed alternative monitoring arrangements to be made without a protocol amendment (if site level schedules were specified in the protocol). The risk assessment and/or monitoring plan may need to be adapted with the acceptance of some risks which would under usual circumstances be mitigated by on-site monitoring review. Critical data points should be risk assessed for likelihood of error and if errors occur whether they could be detected via a centralised monitoring method or accepted. Errors may also be picked up without the need to see the source data and can be checked by real-time review of data entered into the eCRF by CTU staff and where obvious errors are noted, or missing critical data are identified, this can be clarified directly with the trial site. Where these risks cannot be accepted or mitigated in this way a remote monitoring method is necessary which may include remote SDV

or SDR. Remote monitoring can be achieved a number of ways but relies heavily on site input and is, therefore, limited by site capacity. Table 2 summarises remote monitoring methods and the authors' experience of these.

Table 2
Remote monitoring methods for SDV and other checks

Remote Monitoring Method	Experience
Direct Access to Site Electronic Medical Record provided to the monitor	Direct access to patients EHR (Electronic Health Record) away from the site creates issues around confidentiality and is only feasible where the HER was set-up with such access in mind. Consideration needs to be given on where access takes place, for example will monitors be accessing records in an open plan office, public space or other location where others who are not authorised could view sensitive information. Host organisations and sponsors (with input from their Caldicott Guardian if applicable) need to provide explicit instructions on what can be accessed where, and an agreement from the monitors that this will be complied with. Access from home can be acceptable, provided that there is somewhere private that this can be done, away from family etc. The device through which this is accessed must have adequate security, such as adequate firewalls, secure log-in and passwords etc, and must not be left unattended and accessible. The instructions should not allow printing, emailing or downloading of any records, or this should be disabled within the system. See MHRA guidance (10). Our recent experience is that this has been possible for one UK NHS Trust. This method is highly effective and does not cause a high burden for trial sites as monitors can access the data and perform review without site staff input, other than IT providing access and for addressing critical issues at the end of the review.
Provision of pseudonymised source documents	Only provided for a very small amount of data and trials. High burden for sites to redact source data and open to errors in redaction and copying. EMA guidance states that documents monitored in this way need to be rechecked on-site.(11)
Videoconferencing, site staff use a secure conferencing platform and screen share the view of the health record with the monitor.	No experience to date but some trial sites are considering this where it is not possible to provide the monitor with direct access to the electronic health record. As site staff will need to access the record and share their screen during the whole review this is a high burden to sites. There is also anecdotal experience that some sites do not allow use of videoconferencing due to data protection concerns and NHS local policies on video conferencing; there is site variation on which systems may be permitted (if any).
Monitoring by phone*	Phone conversations using a monitoring checklist can be useful but are reliant on sites having capacity. Source documentation is not specifically being reviewed, but the discussion can provide the opportunity to identify concerns and support the site.
Questionnaires, site quality control checklists and essential documents sent by the site to the monitor	Limited, due to site capacity for completing checklists and scanning and emailing documents. Found to be useful for IMP accountability and acceptable to sites where pharmacy resource was not redeployed.
* SDV not possible by this method	

Consideration also needs to be given to the process of triggering on-site monitoring visits. Where these visits will not be possible, alternative actions will need be taken such as telephone contact with site staff to assess compliance / issues and other remote monitoring activities (Table 2).

Table 3 gives more detail on phone and videoconference remote monitoring

Table 3
Working example of monitoring using phone and video conferencing

Action item	Aim	Monitor's Actions	Comments
1	Decrease the requirement for site level monitoring; by implementing alternative monitoring mitigations	TC or email site staff (PI team) to ask if/when they are available for a TC or VC in place of an on-site monitoring visit AND what data could be shared with the monitor ahead of this virtual meeting.	Use video conferencing if the site has the IT access. If not, then a TC. Ensure monitors have the flexibility to meet with site staff when it is convenient for the sites.
2	Prioritise patient safety, outstanding site actions and data integrity of the study primary end-point for remote monitoring	Develop a template tracker to ensure the minimum safety & primary end-point data are discussed in the TC/VC.	Put the questions in priority order for the TC/VC.
3	Give the site as much time as possible to prepare* *Note that for COVID-19 studies; sites should be informed of and agree to the minimum data they will be asked to supply for remote monitoring, where employed.	Request appropriate documents ahead of the meeting – keep this to a critical minimum.	This could include investigator site files (ISFs); delegation logs; primary end-point pseudonymised source data.
4	Conduct a successful site TC/VC.	Review appropriate documents ahead of meeting.	In line with preparation for all monitoring visit types
5	Prioritise the discussion with site in case the call is cut short by technical problems or a local emergency.	Use the template tracker completed with all actions required of site & prioritise the TC/VC discussion accordingly.	Discuss the timing of next remote visit

TC: teleconference; VC video conference; CI Chief Investigator; PI Principle Investigator

It may also be possible that sites, particularly those experienced in early phase work, may be able to perform SDV within their usual process and experience. We have experience of sites, for COVID-19 trials, taking on the SDV task in this way, utilising independent staff and a robust process.

For trials in set-up where remote monitoring is planned upfront, this should be reflected in the protocol, risk assessment and informed consent.

Action item	Aim	Monitor's Actions	Comments
6	Manage any resulting issues	Escalate any unreported SAEs, missing visits, major deviations impact on patient safety/data integrity of missing visits.	Quality, CI, PI, stats and sponsor may need to be consulted. Update study risk assessment with site-specific issues and/or availability during COVID-19 outbreak. Consider what appropriate actions, if necessary should be undertaken
7	Complete the monitoring visit report (MVR) and site f/up letter.	As normal.	No comments.
TC: teleconference; VC video conference; CI Chief Investigator; PI Principle Investigator			
It may also be possible that sites, particularly those experienced in early phase work, may be able to perform SDV within their usual process and experience. We have experience of sites, for COVID-19 trials, taking on the SDV task in this way, utilising independent staff and a robust process.			
For trials in set-up where remote monitoring is planned upfront, this should be reflected in the protocol, risk assessment and informed consent.			

Monitoring without on-site or remote monitoring option

In the setting of a global pandemic, the use of remote monitoring methods may be limited or even impossible due to lack of research staff time. In this situation focused risk-based monitoring may be considered. With this method of monitoring the sponsor should identify the key risks involved with the trial and develop a centralised method of reviewing these risks. Primarily the focus should be on patient safety, primary outcome measure data and any other data considered critical. An example from one CTU was to focus on data relating to patient safety. Data relating to adverse events and protocol deviations were collated and reviewed at monthly Trial Management Group (TMG) meetings where the frequency and type of events as well as the quality of the data submitted was considered. Anything which raised concern with the TMG triggered a telephone call with the site principal investigator, and further investigation was carried out if necessary. A Data Monitoring Committee (DMC) was also convened monthly with the aim of independently reviewing safety data. This method requires timely submission of data from the site so emerging triggers can be quickly identified.

Note that monitoring of all studies during the COVID-19 pandemic is likely to lead to deviations from and updates to the monitoring plan due to changing conditions. Notes to file, monitoring mitigations and SOP deviations need to be discussed with the CTU's Quality Assurance (QA) team, and Monitoring Visit Reports (MVRs) must accurately state the reason why no/reduced/outside of agreed window of monitoring has occurred. Study risk assessments should be updated and discussed with QA teams, CIs & sponsors.

Minimising data

A number of COVID-19 trials have been developed and set-up with the knowledge that on-site monitoring will not be possible. Many of these are Clinical Trials of an Investigational Medicinal Product (CTIMP) intended to support marketing authorisations, which would usually require a high level of on-site monitoring. As this may not be possible for the foreseeable future, consideration of alternative methods for data review and verification will have been considered, as discussed above.

Due to the potential for placing an increased burden on participating sites that some remote monitoring methods may pose, coupled with the need to be confident in the completeness and accuracy of data, one important consideration is the quantity and complexity of the data requested.

The collection of non-essential data has long been known to increase the burden on both participating sites and sponsor teams, and this is now starting to be quantified. Recent data from Fougerou-Leurent et al (12) suggest that only 13% of the data collected are critical data items and Crowley (13) at al found 5% of items were for the primary outcome of the trial.

If the data collected can be reduced to that which is considered critical, this will reduce the burden on sites for CRF completion and sponsor teams for monitoring. The reduction in data collection also has wide-reaching benefits for the sponsor including simplified and more rapid CRF and database development, more efficient data management and statistical analysis and most pertinent to this review, fewer data points for which monitoring is required. RECOVERY-RS reduced the data collection to be as simple as possible, via agreement between the Trial Management Group (including the trial statistician), programming team and QA team.

If the COVID-19 pandemic can bring one benefit to clinical research in the long-term, minimising data collection would be a wide reaching, mutually beneficial process improvement.

Although the requirement for data minimisation is well established and embedded within the Data Protection Act, 2018, the pandemic situation has encouraged trial development teams to consider data minimisation far more than they may have done previously. This was largely due to the pandemic clinical impact, when site staff were excessively busy so minimising data as much as possible was essential.

The role of the sponsor (as data controller) in guiding through policy, training, provision of eCRF platforms, review, etc., is absolutely critical (including where this level of oversight is carefully delegated to, e.g. a CTU) not only to the efficient delivery of research, as described here, but also for the sponsor to meet its legal obligations.

Altered data collection and retention

Limiting paper contamination within COVID-19 areas, as well as clinical trial burden due to the reduced staff resource at participating sites, has required other adaptations in how trials are managed. Examples from COVID-19 trials have included the completion of validated Patient Reported Outcome Measures (PROM) tools via the phone rather than patients completing the forms directly. This could be done by research staff at sites, or by CTU staff if patients have given consent for this.

COVID-19 trials also presented additional consideration when discussing where and how patients were identified and confirmed as COVID-19 positive. This was partially due to the rapidly evolving national situation around screening; availability of screening and false negative rates, and also how patients were managed once eligibility was confirmed as patients not requiring clinical care were discouraged from attending hospital settings. These issues present challenges for monitoring.

At a sponsor or central level, Trial Master Files (TMF) are often paper based. With many CTU staff moving to a home based working arrangement, mitigations have needed to be made. In some instances this has involved consideration and implementation of electronic TMF.

Site set up changes

Although some CTUs have previously carried out site initiation visits (SIVs) using video conferencing facilities instead of on-site visits, during the COVID-19 pandemic this has become the only solution for site initiation. The basic structure is similar to face-to-face SIVs with a comprehensive slide set, live presentations by the clinical and trial management teams, and an opportunity for questions. The familiar structure enables a trial team to develop materials in an established way, but to then adapt the delivery to suit the current environment. Sites also benefit from the questions that another site thinks to ask.

In the RECOVERY-RS trial a large site-set up team was established, and SIVs were conducted every weekday at three time slots per day. Time slots were advertised to sites with booking details. This was cost and time-efficient for the trial team and for site staff, and enabled multiple sites to receive a SIV simultaneously. It also enabled multiple site staff to attend different SIV slots, from numerous locations, fitting in with workload and availability. With clear guidance on the meeting conduct, a separate member of the team managing the video conferencing admin, and questions posted via the 'chat' function, meetings ran smoothly and replicated a face to face meeting as much as possible.

Risk proportionate approaches should always be used to ensure oversight of adequate experience and training of site staff, and the current situation can provide an opportunity to tailor the oversight more specifically to each individual trial. It may not always be necessary to collect CVs and GCP certificates for all (or any) site staff, if the PI or R&D department can confirm they are held on site. The PI is responsible for their research team being trained and experienced in their role. Equally, a hierarchy of study-specific training requirements may be implemented to request a core set of study training to be completed and signed off by the PI only, with PI oversight to confirm site staff have appropriate training to perform their role within the trial. Websites can be a useful tool to provide and record training and also act as a document repository, alongside a website's traditional remit of trial promotion. Training materials can be available for sites to access electronically, with the ability to 'sign off' training modules online removing the need for paper copies, simultaneously providing central oversight of each site's training status (and potentially removing the need for a separate delegation log). This facilitates local site set-up, enabling work to be done at individually convenient times, without the need for printing facilities or transfer of paperwork.

Speed of trial development

Many CTUs redirected resource to COVID-19 trial development and staff have worked at pace, contributing many hours in a short time, collaborating with many individuals and organisations (pharma, laboratories, clinicians, government) to pull together and fast track trial ideas into solid trial proposals, creating protocols in just a few weeks. Throughout the process the MHRA and HRA have been available for early discussion, prior to submission, to ensure approvals can be swift following submission. In most cases MHRA and HRA approvals have been issued in a matter of days including national holidays. There have also been additional steps that COVID-19 trials have needed to navigate, the primary one being Urgent Public Health (UPH) priority approval which ensured sites prioritised work on COVID-19 trials with high priority questions as deemed by the government. Due to the overwhelming demand for UPH approval, their review was sometimes conducted in parallel with MHRA and HRA review in order to maintain trial set-up momentum.

Due to the speed of set-up, trial teams, including monitors, have been required to fast track trial risk assessments and the subsequent trial monitoring plans, including considerations of mitigations due to site access restrictions and minimised site resource requirements. There was little precedence for this in the UK at the time, meaning many sponsors were 'thinking on their feet' to provide pragmatic solutions to emerging and evolving challenges.

Early phase trials have been required to review Safety Review Committee (SRC) processes, as usual practice is complete SDV of the data being discussed which inform dose escalations. Trial specific mitigations have been considered (e.g. site performing SDV as described previously).

Whilst there have been significant achievements with developing complex trials in an expedited manner, there are some less positive aspects of the process. Accelerated protocol development and trial set-up processes have required a substantial resource allocation, which in most cases has been delivered by experienced staff working evenings and weekends for prolonged periods. Similarly, once approved the trials have required frequent amendment to account for the changing pandemic landscape, emerging safety information and differing processes across healthcare settings. The impact of these on the risk assessment and monitoring plans make this challenging for sponsors, CTUs and sites to manage.

Impact on non COVID-19 portfolio

Many sponsors and sites suspended recruitment into open trials at the start of the pandemic, and sites participating in open trials decided if patients already recruited into trials were able to continue treatment and follow-up. A risk-based approach was implemented and protocol processes were reviewed. Examples include clinician/patient phone calls rather than hospital clinic visits; transfer of patient care to alternative healthcare providers; provision of IMP to patients at home and use of validated safe-boxes for the return of samples via post. These actions have required changes to central monitoring of data, for example a metric alarm threshold for deviations would need to be increased. Often, SDV of data has been stopped with monitoring defaulting to central and remote monitoring, but this is expected to recommence as conditions permit.

Lastly, as sponsors and CTUs plan for trial restart, they should consider COVID-19 impact trial viability assessments which address if/how the trial population, interventions, and outcomes have been impacted to

inform if trials are able to re-open or not, and whether any changes are required. Early and open engagement with the trial site staff and the R&D office is important. Trial opening and change decisions may require trial risk assessments and the data monitoring plans to be updated. Sites need to commit to the necessary monitoring and if the site cannot, then consideration may need to be given to keeping the site on hold to recruitment; this capacity review will often form part of the site level risk assessment, which are likely to be required prior to re-opening(14).

Discussion

With the arrival of COVID-19 in the UK and the need for COVID-19 trials to be rapidly created and start recruitment, monitoring aspects of trials had to develop at speed in the UK and similarly throughout the world. Changes were made to how consent was obtained, what data were collected and the method of setting up sites. Risks were thought about within the new climate to enable monitoring without site visits or undue burden to the sites. Many of these changes could continue. For all future trials sites could access the training at a time of their convenience and this could be recorded electronically, with the PI notified so that they can delegate tasks in an informed manner. For trials with many sites, site initiation visits could be done at regular times with personnel joining when they are able. Data sets should be minimised and patients could use on-line eConsent. With monitoring, it could be recommended that we reconsider our over reliance on on-site monitoring and more research effort could be focused on optimising central monitoring so that the site burden is minimised. As electronic patient record systems evolve, if sites could ensure that their electronic patient record systems are able to offer remote access restricted to specific trial participants, monitoring would be enabled. If this is not possible in the short term, sites organisational risk assessments could take place to allow access to be given in the interim with data protection principles upheld.

The speed and efficiency of COVID-19 trial setup from the CTUs was complemented by the matched speed of assessment from the HRA, MHRA and UPH. It should be noted however that the intense speed of set-up came at the cost of CTU staff working very intense hours, and multiple protocol and document amendments which is inefficient and undesirable outside of the pandemic situation. Some aspects of efficiency could continue; examples include efficient document creation using learnings from COVID-19 trials (e.g. consent options), minimising data collection, development of database library documents and eConsent, better understanding of SIV options.

The announcements on clinical trial conduct from the UK Government (15), HRA (16) and EMA (11) were helpful though not exhaustive. CTU staff needed to interpret these and make decisions for their own CTUs.

Our paper only reports the experience from nine UKCRC registered CTUs and only on the monitoring aspect of trial conduct. The differences for non-CTIMP and Scottish regulations have not always been explicitly stated. However, we hope it helps others setting up COVID-19 or other pandemic trials and gives some material for consideration of changes to the conduct of clinical trials

Conclusion

We have described our experience of running COVID-19 trials and explained our monitoring practices. We hope many of these efficiencies will continue to be used in future trials.

Abbreviations

CI – chief investigator

CRF – case report form

CTIMP- clinical trial of an investigational medicinal product

CTU- clinical trial unit

CV – curriculum vitae

DMC – Data Monitoring Committee

eConsent - use of any electronic media to convey information and to see and/ or document consent via an electronic device

eCRF – electronic case report forms

EMA- European Medicine Agency

FDA – Food and Drug Administration

GCP- good clinical practice

HRA – Health Research Authority

ICF- informed consent form

ICH - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IMP – investigational medicinal product

ISF – investigator site file

MHRA - Medicines and Healthcare Products Regulatory Agency

mNCA – model non-commercial agreement

MVR- monitoring visit report

NHS - national health service

NIHR – national institute for health research

PI – principal investigator

PeLR- Personal Legal Representative

(ProfLR)-Professional Legal Representative

PROM – patient reported outcome measure

QA – quality assurance

RCT – randomised controlled trial

Red zone – restricted area for patients with COVID-19

SAE – serious adverse event

SIV – site initiation visit

SDR- source data review

SDV- source data verification

SRC – safety review committee

TC - teleconference

TMF – trial master file

TMG – trial management group

TMP – trial monitoring plan

UKCRC – United Kingdom Clinical Research Collaboration

UPH - Urgent Public Health Priority

VC – video conference

Declarations

- Ethics approval and consent to participate

Not required as all information given from authors CTUs.

- Consent for publication

Not applicable

- Availability of data and material

Gavin Perkins and Danny McAuley (RECOVERY-RS Co-Cis) have agreed to referencing RECOVERY-RS.

- Competing interests

The authors declare that they have no competing interests.

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- Authors' contributions .

AC first voiced the idea of getting our experience out to others. SBL led the paper writing. All authors gave ideas of sections during a discussion, each contributed to the paper writing and reviewed the last version of the manuscript.

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- Authors' information

All authors are core members of the UKCRC Task and Finish Monitoring Group which aims to push forward several aspects of monitoring.

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