Abstract

Introduction: As clinical trials were rapidly initiated in response to the COVID-19 pandemic, Data and Safety Monitoring Boards (DSMBs) faced unique challenges overseeing trials of therapies never tested in a disease not yet characterized. Traditionally, individual DSMBs do not interact or have the benefit of seeing data from other accruing trials for an aggregated analysis to meaningfully interpret safety signals of similar therapeutics. In response, we developed a compliant DSMB Coordination (DSMBc) framework to allow the DSMB from one study investigating the use of SARS-CoV-2 convalescent plasma to treat COVID-19 to review data from similar ongoing studies for the purpose of safety monitoring. Methods: The DSMBc process included engagement of DSMB chairs and board members, execution of contractual agreements, secure data acquisition, generation of harmonized reports utilizing statistical graphics, and secure report sharing with DSMB members. Detailed process maps, a secure portal for managing DSMB reports, and templates for data sharing and confidentiality agreements were developed. Results: Four trials participated. Data from one trial were successfully harmonized with that of an ongoing trial. Harmonized reports allowing for visualization and drill down into the data were presented to the ongoing trial’s DSMB. While DSMB deliberations are confidential, the Chair confirmed successful review of the harmonized report. Conclusion: It is feasible to coordinate DSMB reviews of multiple independent studies of a similar therapeutic in similar patient cohorts. The materials presented mitigate challenges to DSMBc and will help expand these initiatives so DSMBs may make more informed decisions with all available information.
DSMBs looking at a single study benefit from the context of other study findings in a similar therapeutic area to fully understand the scientific landscape. In fact, the Code of Federal Regulations Title 21 Section (c)(1)(i)(c)(ii) states, “The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies . . . whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug” [11]. The FDA 2021 guidance for safety reporting notes the requirement for an aggregated analysis has the benefit to allow sponsors (and by extension DSMBs) to meaningfully interpret safety signals of investigational therapeutics [12]. Research suggests DSMBs should exercise patience when a small study shows positive or negative signal, especially if the signal from multiple studies is discordant [2, 4]. Conversely, DSMB confidence in reviewing stopping rules for a specific study can be enhanced by understanding there is directional concordance with other studies in the same therapeutic area [2, 4].

In our experience, DSMBs sometimes request prepublication trial results from similar studies so that decisions can be made based on the totality of available evidence. Consequently, the National Center for Advancing Translational Sciences (NCATS) Trial Innovation Network (TIN) investigators sought to formalize a method by which independent DSMBs, each overseeing independent studies of similar therapeutics in a similar disease setting, could share their data while maintaining autonomy, preserving their primary role in individual study oversight, and protect the confidentiality of the studies.

Extending beyond a mechanism for sharing DSMB reports, many clinical trials report a similar set of elements to the DSMB (e.g., accrual, adverse events, outcomes) creating an opportunity to combine data. Collating common reporting elements into a single, consistently formatted report has the potential to provide greater context and actionable information. We, therefore, sought to extend freely available visualization and data reporting tools to enable the generation of a harmonized DSMB report compiling information from multiple independent studies, with subsequent delivery to each study’s independent DSMB via a secure, digital platform. Combining a digital format with modern statistical graphics provides DSMB members with a tool to further evaluate individual-level data and to investigate the safety and efficacy signals from the participating studies without breaking any study’s blind.

Here, we describe the systems, processes, and tools that were developed to complete this DSMB Coordination (DSMBc) initiative. Challenges to the sharing of harmonized DSMB reports are described, as well as strategies for overcoming them.

Methods

The DSMBc effort was initiated in July 2020 leveraging a set of Convalescent Plasma randomized-controlled trials (RCTs) as these studies were actively accruing and overseen by DSMBs that could benefit from the sharing of intermittent safety and efficacy data. From March 1, 2020 to June 1, 2020, thirty-three RCTs utilizing SARS-CoV-2 convalescent plasma for the treatment of SARS-CoV2 were identified on ClinicalTrials.gov as registered in the United States [13]. Initially, three RCTs were identified as being potentially informative to the overall drug effect question. The Convalescent Plasma to Stem Coronavirus (CSSC-001) (NCT04323800) outpatient trial enrolling asymptomatic high-risk subjects who experienced a close contact exposure to a person with COVID-19 in the last 120 hours, target N = 500 [14] and the Convalescent Plasma to Limit Coronavirus Associated Complications (CSSC-004) (NCT04373460) outpatient trial enrolling COVID-19 symptomatic subjects with a positive by RNA detection test for SARS-CoV-2, target N = 1344 [15] were both led by investigators at Johns Hopkins University. The third study, the Passive Immunity Trial for Our Nation (PassItOnII) (NCT04362176) enrolling symptomatic inpatient subjects with laboratory-confirmed SARS-CoV-2 infection, target N = 1000 [16] was led by investigators from Vanderbilt University Medical Center (VUMC). We initially selected the two CSSC trials for DSMBc as they were investigating the same therapeutic in comparable patient populations and were concurrently accruing. We posited that data from these two studies could be successfully harmonized as they were both outpatient studies with similar outcome measures.

In October 2020, a fourth international RCT was identified, the CONvalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness (CONCOR-1) (NCT04348656) inpatient trial enrolling participants with confirmed SARS-CoV-2 infection receiving supplemental oxygen, target N = 1200 [17]. We added the CONCOR-1 trial as a direct comparator to the PassItOnII study since both were inpatient trials with similar accrual goals and outcome measures.

There was some overlap in personnel between the DSMBc initiative and the PassITOnII trial as disclosed in the Acknowledgements section of this manuscript. The CSSC studies shared a single DSMB but had independent data and safety monitoring plans. The PassITOnII and CONCOR-1 DSMBs were each fully independent.

Initial Engagement

To obtain agreement from clinical trial principal investigators (PIs) and DSMB members, a DSMBc virtual meeting was scheduled with the PIs of the three initial trials (PassITOnII, CSSC-001 and CSSC-004). The goal of the DSMBc initiative was introduced, with emphasis that collaboration would be needed to share information, that transparency among studies would be paramount, the confidentiality of data would be critical, that allowing each study to achieve its own rigorous scientific answer was a priority, and sharing data as studies continued to accrue results (rather than only at the end of a given study) would be essential to DSMBc activities. A second virtual meeting was then held to introduce the project to the DSMB chairs of each trial. The result of these initial meetings was the development of a DSMBc process map to describe the three different phases needed for the DSMBc initiative: onboarding; secure data access; and generation/sharing of DSMBc harmonized reports. The process maps delineating responsibilities during each phase, the secure flow of data, and the process for sharing the DSMBc harmonized report are publicly available at https://rocket.app.vumc.org/index.php?doc_id=31371. The detailed approach for DSMBc data sharing procedures and the processes for report creation and verification are described in our Standard Operating Procedure (SOP), which are available in the supplementary materials [Supplemental Appendix 1].

Regulatory and Contractual Agreements

The DSMB Coordination for COVID-19 initiative was approved as exempt research under 45 CFR 46.104(d)(4) by the VUMC Human Research Protections Program [18]. Data Use Agreements (DUAs) were executed between VUMC and Johns Hopkins University to acquire copies of the CSSC-001/004 protocol, consent forms, case report forms (CRFs), data dictionaries, DSMB charters, and...
clinical trial data. Because the PassItOnII clinical trial was sponsored by VUMC, DUAs were not required for these study materials. Each study team reviewed the consent forms for the trials to confirm they allowed for the sharing of study data.

The DSMBc initiative did not overlap with any oversight activities that might be described in a DSMB Charter. The DSMBc serves as honest brokers, intended to support, and not supplant the usual DSMB operations. A DSMBc Report Sharing Agreement was developed and subsequently executed to address several key issues, such as how the DSMBc report would be distributed to the individual trial DSMBs, the data sharing and retention policy, the conflict-of-interest acknowledgement, the confidentiality policy, and a breach clause (a template is provided in Supplemental Appendix 2). The data retention statement indicated that the DSMBc could use the individual study data as long as necessary to implement, administer, and manage the harmonized reporting efforts of the DSMBc initiative, which could extend beyond the life of an individual study. The agreement also noted that the individual study data and reports would be retained up to 2 years following the conclusion of study recruitment and DSMB activities of all studies, at which point the study data would be destroyed unless otherwise directed by the FDA.

Data Acquisition

To minimize the burden of providing trial data for the harmonized report, study teams were invited to upload their raw data to a central portal without modification for central harmonization. The time required to map data elements to a common data model had been identified as a barrier to participation during engagement activities, so DSMBc biostatisticians harmonized the data centrally.

The secure file upload application in the Research Electronic Data Capture (REDCap) system [19] was utilized by individual study personnel for secure data transfer. Managing REDCap user rights allowed us to restrict user access and permissions to ensure that blinded statisticians, including the one at VUMC, remained blinded to all data presented with treatment assignment. Acceptable formats for the uploaded data included R, SAS, SPSS, Stata, CSV, or Excel format. As appropriate, a file specifying the data format was also uploaded. In addition to the data, a copy of the study interim analysis report was requested. Alternative approaches for data sharing were considered, such as utilizing an established public (trial) data repository. This approach was not pursued because of confidentiality concerns and because it was not clear how to keep some team members blinded to treatment assignments while allowing others to be unblinded. While a public repository specifically suited to the needs of future DSMBc may become available, this was beyond the scope of this proof of concept.

Acquiring the protocol, case report forms, data dictionary, DSMB charter, and DSMB report shell well in advance greatly informed the process for harmonizing data, allowing the DSMBc biostatisticians to identify the relevant enrollment, eligibility, demographic, safety, and outcome variables for the final harmonized report. In addition, mock data from within the CSSC-004 trial electronic data capture system were provided to facilitate variable mapping. The mock data set allowed the statisticians to prepare the necessary code to harmonize in advance of receiving raw trial data, and we recommend the provision of this mock data file as an efficiency measure. Even given this advanced preparatory work, data sharing needed to occur at least three weeks prior to providing any DSMB with a harmonized report to ensure sufficient time to generate the harmonized report and review it with the statisticians of the collaborating trials.

Statistical Analysis Approach

The goal for the DSMBc harmonized reports was not to replicate the individual study interim analysis plans, but to characterize those data that could be mapped across study groups, such as baseline data, safety data, and occasionally efficacy data. These were displayed using interactive statistical graphics offering both high-level summaries and individual patient data. The interactive, harmonized reports provided a synchronized review of data from multiple studies with the following items:

- Subject accrual, accounting for regions, countries, sites
- Descriptive statistics for baseline and longitudinal data
- Event report for binary events such as serious adverse events
- Number-at-risk report (declining denominators for longitudinal data)

The detailed harmonized reports featured interactive graphical elements to explore patterns as well as to read individual data off the graphics. Graphic elements include spike histograms, extended box plots, multiway dot plots, and trend line plots. The harmonized report was created with the hreport package in R (hbistat.org/R/hreport), which can be used to create an interactive html report with R markdown [20].

To minimize the risk of inadvertently unblinding the data, the DSMBc Report Sharing Agreement explicitly stated that reports would be made available to the individual study DSMBs only during their closed meetings and only in executive session when attendance is limited to the voting DSMB members. To restrict distribution of the report outside of the individual DSMBs, the harmonized reports were presented in a format that prevented downloading and a statement was prominently displayed in the report that the data contained therein was unmonitored and interim and could not be downloaded or shared. Finally, the confidentiality statement in the DSMBc Report Sharing Agreement signed by all DSMB members stated that all data and materials submitted to the DSMBc group and DSMB members of participating studies will be kept confidential, will not be downloaded from the secure server on which they are provided, and will not be disclosed to anyone except as required by law, or to the extent necessary to evaluate the harmonized report. Each DSMBc and DSMB member of participating studies agreed to use appropriate safeguards to protect the confidentiality of shared data and prevent unauthorized use or access to the data.

To allow for secure access to the reports, the DSMBc honest brokers created a custom portal [21]. This allowed the DSMBc group to control user access to the reports through password protection and account management, ensure the successful file upload of reports, and allow for the sharing of user support materials (e.g., sample reports: How-To Quick Guides, and instructional videos). The DSMBc portal was designed to accommodate three different user roles with varying access rights and permissions (Table 1). The Administrator role had the broadest permissions and was limited to select members of the portal application development team. The Data Manager role was designated for DSMBc staff and allowed access to all projects and reports, but with more limited permissions. This was the role utilized by DSMBc biostatisticians who were responsible for generating and uploading harmonized reports. The Personnel role had the most restricted access and
was limited to all other users, including the DSMB members, PIs, and study statisticians of the participating trials. Early feedback from DSMB members identified a need for a feature that would allow users to document comments and notes on their own individual digital copy of the harmonized report for later reference and archiving in the DSMBc file. In response, we developed a portal feature that supports both private and shared (among DSMB members) comments and notations.

Integrating CONCOR-1

In October 2020, during the variable mapping of the two CSSC trials and the PassItOnII trial, the PI of the CONCOR-1 RCT expressed interest in participating in the DSMBc initiative. Within 9 weeks, the CONCOR-1 team formally agreed to participate, shared their study materials (protocol, data dictionary, consent forms, case report forms, and DSMB charter), confirmed preliminary DSMBc harmonized report data mapping, and shared a mock data set. However, it took an additional 11 weeks to execute a Data Use Agreement to allow for the sharing of actual trial data. During this time, the independent data and safety monitoring committee for CONCOR-1 recommended that the trial should stop enrollment as it had met the predefined threshold for futility. However, the CONCOR-1 PI was committed to sharing their final interim analysis data with the DSMBc initiative. The interim data were shared on 2 March 2021.

Progress

The DSMBc initiative successfully engaged the study teams and DSMBs of four randomized clinical trials investigating the use of convalescent plasma for the treatment of Sars-CoV2. Data Use Agreements were executed with three of the four trials; the fourth trial did not require a DUA as it was institutionally co-located. Protocols, consent forms, case report forms (CRFs), data dictionaries, and DSMB charters were acquired from all four trials. A timeline for the initiative is shown in Fig. 1, which shows our progress to date, and which demonstrates the complexity of

Table 1. Data and Safety Monitoring Board Coordination (DSMBc) Portal user roles and permissions

| DSMBc portal permissions | Administrator | Data Manager | Personnel |
|--------------------------|---------------|--------------|------------|
| Access to all projects and reports | ✓ | ✓ | ✓ |
| Access to specific project and corresponding reports only | ✓ | ✓ | ✓ |
| Ability to manage users, projects, reports | ✓ | ✓ | ✓ |
| Ability to add comments | ✓ | ✓ | ✓ |
| Ability to read all comments | ✓ | ✓ | ✓ |
| Ability to read public comments only | ✓ | ✓ | ✓ |
| Ability to update all comments | ✓ | ✓ | ✓ |
| Ability to update own comments only | ✓ | ✓ | ✓ |
| Ability to delete all comments | ✓ | ✓ | ✓ |
| Ability to delete own comments only | ✓ | ✓ | ✓ |

Table 1. Data and Safety Monitoring Board Coordination (DSMBc) Portal user roles and permissions

*Study materials include protocols, case report forms, data dictionaries, consent forms and DSMB charters.

Fig. 1. DSMBc engagement timeline.
coordinating DSMB review among multiple studies with discordant and unpredictable meeting schedules. A detailed visual timeline outlining key steps in the generation of a DSMB report is shown in Fig. 2.

At this time, all participating studies have closed to enrollment. The CONCOR-1 data were successfully harmonized with the PassItOnII data and the harmonized report shared with the PassItOnII DSMB in closed session prior to completing accrual. For the two CSSC studies, all of the administrative, regulatory, and contractual processes were completed and data mapping had been confirmed. However, due to the delayed execution of the JHU DUA, CSSC data were not harmonized since the proof of concept had already been demonstrated via the successful compilation and sharing of a harmonized report with a sitting DSMB making decisions on a trial underway. It was determined the opportunity cost to dedicate more effort without the possibility of the harmonized report having any impact on an existing trial was too high. Due to meeting the threshold for futility, the CONCOR-1 DSMB completed their deliberations without reviewing a harmonized report, although they requested to review the report after the trial data were unblinded to provide feedback on its potential utility and whether it might have helped their decision making.

**DSMB Member Feedback**

Of the three main DSMB reporting domains (baseline characteristics, safety, and outcomes), DSMB members reported that the additional safety data offered in the harmonized report was most helpful. DSMB members recommend careful attention be paid to whether the safety data being compared was being purposefully and actively tracked across each of the contributing studies; absent systematic collection of safety data, misinterpretation of safety signals would be likely. In addition, DSMB members commented that the baseline characteristics provided an opportunity to compare similarities and differences in the cohorts enrolled in the trials. Outcome data were reported to be the least helpful section.

The DSMBc initiative required the collaborative efforts of research teams, the implementation of administrative processes, and the development of new tools for data and report sharing and for generating harmonized reports. Our project demonstrates that all of these steps are feasible. Our experience also identified the considerable challenges that must be overcome for the benefits of DSMBc to be realized. We have summarized these challenges, and the stakeholders associated with emphasizing the challenges, in Table 2. The main solutions implemented to overcome these concerns were introductory meetings to detail the initiative, providing information and contractual agreements about data sharing and how data are managed and controlled, and the use of a DSMBc portal serving as a secure honest broker.

**Table 2. Stakeholder-identified barriers and solutions to data sharing for harmonized reports**

| Concerns          | DSMB Chair | DSMB Member | Principal Investigator | Study Statistician |
|-------------------|------------|-------------|------------------------|--------------------|
| Security of data  | ✓          |             |                        |                    |
| Confidentiality   | ✓          | ✓           |                        |                    |
| Unblinding        | ✓          | ✓           | ✓                      |                    |
| Public data sharing | ✓      | ✓           |                        |                    |
| Authorship        |            | ✓           |                        | ✓                  |

Key: DSMB – data and safety monitoring board.

**Discussion**

Coordinating DSMB review among independent DSMBs of independent studies with a harmonized DSMB report containing information from all studies is feasible. This work provides a starting place for discussions about the additional value DSMBc might provide given the additional effort that it requires.

**Data to Include**

Our DSMB initiative was a coordinated effort between research institutions, each of which was leading a trial on the effect of convalescent plasma in COVID-19 patients. Implicitly, a prerequisite for a DSMBc initiative is that at least two trials simultaneously investigating the same (or similar) intervention in a comparable patient population. If such a setting exists, as it did during the COVID-19 pandemic, then DSMBc provides a mechanism for DSMB members to examine summaries about the patient characteristics, safety events, and outcomes from the ongoing or recently completed comparable trials. Potentially, DSMBc can provide beneficial aggregated safety data for the review of therapeutics often tested in multisite trials, including PD-1 inhibitors, blood pressure lowering therapies, and oxygen targets in mechanically ventilated patients. In addition, the sharing of data between US only trials and non-US studies can facilitate harmonized reviews of baseline characteristics and safety events to inform decision making in real time. However, we acknowledge the
DSMBc approach is unlikely to fit all programs of research. For example, whether the benefits of a DSMBc would be realized in an industry-sponsored program of drug development is unclear; the proprietary and coordinated nature of such research programs may not warrant a DSMBc approach. Conversely, the process might be especially well suited to broad programs of alike research supported by agencies such as the NIH. While institutional DSMBs often oversee multiple trials, we are not aware of efforts toward data harmonization and joint reporting where appropriate.

At the outset of the current DSMBc initiative, our contention was that providing the additional data would facilitate cross-study comparisons and help inform DSMB decision making about safety and efficacy in individual trials. Our results stem from a single DSMBc initiative and thus reflect only an exemplar about safety and efficacy in individual trials. Our results stem from the study statisticians and the DSMBc honest brokers as they work together to verify the endpoints are calculated correctly. We have provided our standard operating procedure so others may adopt our processes to their own purposes (Supplemental Appendix 1). We believe setting expectations for a DSMB at the outset of a study, such as by describing DSMBc activities in the DSMB charter, may help to facilitate uptake of data harmonization efforts. A major concern for the DSMBc initiative was ensuring consent for data to be used for the proposed purpose, and that confidentiality could be maintained. We recommend that clinical trials consider including language in the consent form that allow for efforts to harmonize trial data and oversight. This will mitigate the need for consent form revisions, submission of amendments to Institutional Review Boards, or re-consenting of subjects to allow for such data sharing. In addition, we also recommend that trials adopt common data elements where they exist (i.e., common variable labels, levels, names and definitions). The use of data standards as proposed by the Clinical Data Interchange Standards Consortium (CDISC) [24, 25] could facilitate harmonization activities and decrease the effort required to map variables across disparate trials, as well as limiting the introduction of errors due to the assumptions made in the harmonization process. Of course, if comparable trials adopt the same electronic data capture system and limited the introduction of errors due to the assumptions made in the harmonization process. Of course, if comparable trials adopt the same electronic data capture system with the same case report form, further efficiencies can be achieved in the harmonization.

Our experience with DSMBc has resulted in a set of proposed processes recommendations for future work in this domain. A list of these recommendations and the benefits they provide in the data harmonization process can be found in Table 3.

Processes

We have provided our standard operating procedure so others may adopt our processes to their own purposes (Supplemental Appendix 1). We believe setting expectations for a DSMB at the outset of a study, such as by describing DSMBc activities in the DSMB charter, may help to facilitate uptake of data harmonization efforts. A major concern for the DSMBc initiative was ensuring consent for data to be used for the proposed purpose, and that confidentiality could be maintained. We recommend that clinical trials consider including language in the consent form that allow for efforts to harmonize trial data and oversight. This will mitigate the need for consent form revisions, submission of amendments to Institutional Review Boards, or re-consenting of subjects to allow for such data sharing. In addition, we also recommend that trials adopt common data elements where they exist (i.e., common variable labels, levels, names and definitions). The use of data standards as proposed by the Clinical Data Interchange Standards Consortium (CDISC) [24, 25] could facilitate harmonization activities and decrease the effort required to map variables across disparate trials, as well as limiting the introduction of errors due to the assumptions made in the harmonization process. Of course, if comparable trials adopt the same electronic data capture system with the same case report form, further efficiencies can be achieved in the harmonization.

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the hreport package, both of which are now available to others seeking to improve trial efficiencies with a secure report management tool.

**Conclusion**

It is possible to share patient-level data between independent DSMBs of ongoing, independent clinical trials. The process was developed using an iterative process and is presented here as a scalable framework for future studies. The next step is to explore opportunities for leveraging DSMBc outside of the pandemic context to potentially shorten the evidence to practice timeline.

**Supplementary Material.** To view supplementary material for this article, please visit https://doi.org/10.1017/cts.2022.387.

**Acknowledgments.** The authors extend their sincere thanks to Drs. Todd Rice (Vanderbilt University Medical Center) and Paul Hébert (Centre Hospitalier de l’Université de Montréal), Drs. Donald Arnold (McMaster University); Philippe Bégin (Centre Hospitalier de l’Université de Montréal), Drs. Jeannie Callum (Kingston Health Sciences Centre), and Keyvan Karkouti (University Health Network, and Sinai Health System) for their data contributions from the PassItOnII trial; Drs. Shmuel Shoham (John Hopkins University School of Medicine), David J. Sullivan (John Hopkins University School of Medicine), and Pablo Tebas (Hospital OfThe University Of Pennsylvania) for their study material contributions from the CSSC-001 and 004 trials.

This work was funded by award number U24TR001579 from the Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH). This work is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

**Disclosures.** The author Christopher J. Lindsell is both a blinded biostatistician on the PassItOnII trial and member of the DSMBc initiative. The author Thomas G. Stewart is both an unblinded biostatistician on the PassItOnII trial and member of the DSMBc initiative.

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