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Traveling the Interstices of Data Sharing

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"We are not cisterns made for hoarding,
we are channels made for sharing."
—Billy Graham (1)

Few topics among researchers have generated as much recent dialogue as the call for clinical trial data sharing. Although a long tradition of sharing data has existed among many trialists, this has largely focused on amalgamating data on similar topics in an integrated meta-analysis in order to provide more confident and precise estimates of outcomes. However, this topic acquired new intensity pursuant to the January 2016 proposal of the International Committee of Medical Journal Editors (ICMJE) to "require authors to share with others the deidentified individual-patient data (IPD) underlying the results presented in the article…no later than 6 months after publication" (2). Furthermore, the editors proposed to make this proviso a requirement for publication in ICMJE journals—effective 1 year after final agreement on this initiative. Implementation proved somewhat more challenging than anticipated. Animated discussion and a diversity of opinions then emerged, culminating in a second ICMJE understatement approximately 18 months later acknowledging, "We have learned that the challenges are substantial and the requisite mechanisms are not in place to mandate universal data sharing at this time" (3). Current ICMJE expectations do, however, require including a data-sharing plan as part of the trial registration process.

Dialogue on this subject continues among a host of interested individuals and groups. In this issue of *JACC: Heart Failure*, Zheutlin and Byrd (4) entreat us to provide "access to others' datasets [to] help early career clinical trialists establish their reputation before they are entrusted with the resources to lead a large-scale trial." They further note that an unreferenced "group of cardiovascular clinical trialists" advocates for 2 years of exclusive access to data, with the implication that such trialists have trepidation about data sharing and seem reserved about potential benefits. One of us (P.W.A.) was part of the ACCESS CV group's perspectives asserting the need for some limitation on access to trial data (5), which remains supportive of open data sharing and has articulated the benefits of this approach. They also provided a comprehensive menu of potential solutions to address the challenges arising from the ICMJE recommendations.

Perhaps this personal view from those of us privileged to work in the cardiovascular arena may provide further context. Large clinical trials are complex organisms that provide a unique opportunity for learning. They often engage thousands of patients, countries in all regions of the globe, and hundreds of site investigators. From inception to protocol design, to assembling the necessary resources, addressing the appropriate regulatory and registration requirements, and operationalizing the multiple teams to conduct the trial, the process commonly requires between 1 to 2 years before the first patient is enrolled. Once recruitment begins, the trial's duration varies depending in part on the desired number of events and/or the minimum period of exposure required. In concert with the trial's inception, a publication charter is commonly established and a series of primary, secondary, and tertiary manuscript topics are proposed. Fundamental to the culture of most successful academic research organizations (AROs) is their inherent generosity of spirit, as manifest by the collaborative opportunities provided to those who contribute to such trials. Broader communication about these pre-planned manuscripts to those interested investigators outside the initial trial perimeter could enhance understanding of what additional work is already intended. Such details could readily be provided in a supplemental appendix to the primary manuscript—this would guide a more informed path to sharing of intellectual capital to enhance scientific progress. The intrinsic

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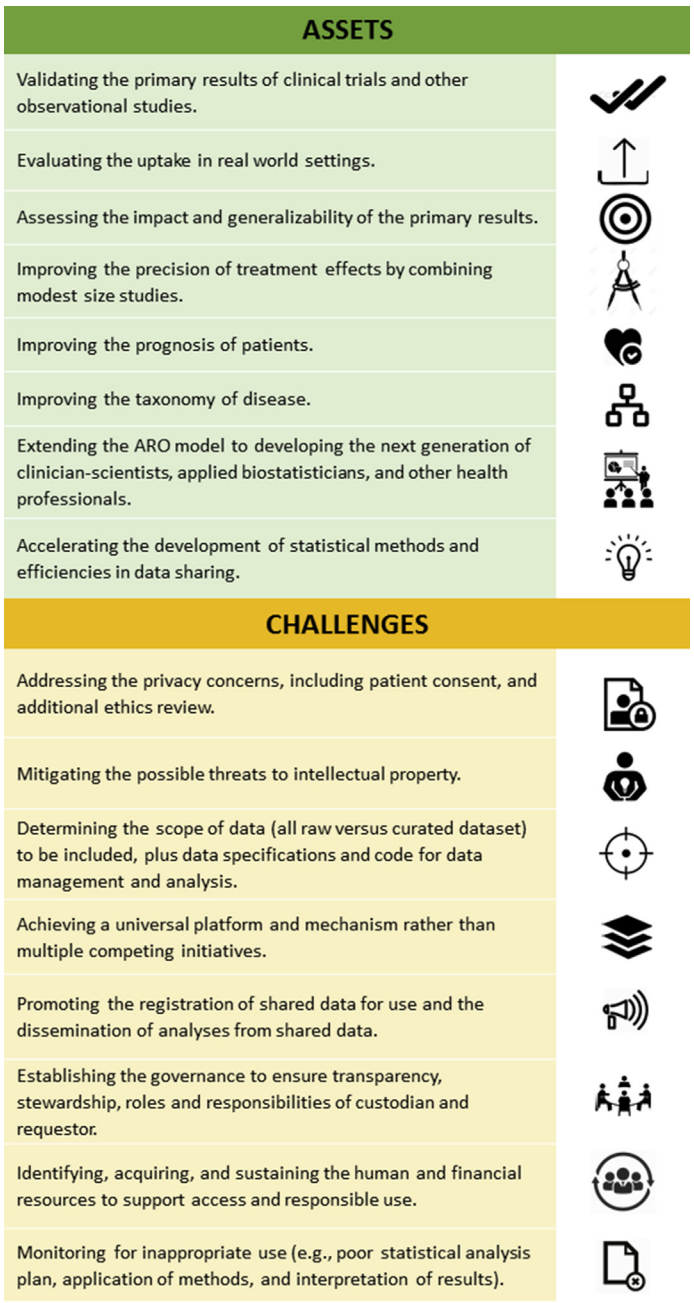
FIGURE 1 Assets and Challenges of Data Sharing



ARO = academic research organization.

serendipity of research findings coupled with probable relevant environmental changes during the course of the trial mandates additional flexibility once the results are known. Before unblinding, it is common to develop an updated statistical analytical plan, and the transparency of this undertaking is required as part of the primary publication process.

A key tenet, woven into the fabric of an ARO, is the mandate to mentor and engage aspiring young investigators at every stage of the trial's evolution (6). Recent examples of sharing opportunities among those who contribute to a trial are evident in the report from the HF-ACTION (Heart Failure-A Controlled Trial Investigating Outcomes of Exercise Training) investigators who published 50 manuscripts in the 4 years after their primary publication (7). Commendably, the authorship of these publications was shared among 137 different individuals (many of whom were trainees) and over one-half of the 82 participating study sites were ultimately engaged as contributors.

Another informative recent example arises from the ASCEND-HF trial (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), which recruited its first patient in 2007 and reported the primary results in 2011 (8). The ASCEND-HF trial continues to provide a robust dataset to inform patient care and the design of future heart failure (HF) trials while also supporting the mentorship of junior investigators. To date, there have been more than 40 secondary manuscripts from this trial: nearly one-half have a first author who was a trainee or junior faculty (<5 years of training). Similar to the inclusive HF-ACTION trial experience, the authorship for the ASCEND-HF trial manuscripts has involved more than 25 individuals as first authors who were not coauthors on the primary publication. The trial leadership has supported the next generation of HF investigators as evidenced by their mentorship of junior investigators transitioning from fellow to faculty and ultimately into senior authorship roles within the evolution of the 7-year study framework. Importantly, this model enhances the seeding, nurturing, and sustainability of academic medicine. Hence, one of the mentees (R.M.) in the ASCEND-HF trial became the mentor for others while still learning from senior colleagues over the 7 years since the primary publication (9,10).

An additional element of the ARO model is the training and mentoring of biostatisticians. As a key part of the investigative team, these skilled professionals are essential in the understanding and analysis of data, and reporting of the results. This becomes especially germane to data sharing, where the learning and appropriate use of new data can be challenging, even for those who return to replicate an analysis originally completed years earlier (11). Partnering biostatisticians from both sides of the data-sharing process serves as a valuable resource to establish and agree upon plans for analysis and subsequent reporting. In addition, the sharing of lessons learned over time provides opportunities to enhance

the quality of statistical analysis, advance new methodologies, and make future data sharing more efficient.

Importantly, sharing data from clinical trials cannot be performed with a one-size-fits-all approach. The complexity of the individual trial and data elements may vary depending on the objectives, that is, investigation of a new product for registration purposes versus a comparative effectiveness study of approved products or procedures. A summary of the potential assets and current challenges to data sharing is provided in **Figure 1**. As we reflect on these, we must continue to honor the ethical imperative to our patients who volunteered to help advance human health by contributing their time and data. Going forward, it would be wise to cast an even broader net to the sharing of patient registries and population health data, because rich collaborative opportunities exist within these sources to: 1) validate the generalizability of clinical trial results; 2) evaluate their uptake and impact; and 3) inform the direction of future research. The Duke Clinical Research Institute's approach to data sharing, SOAR (Supporting Open Access for Researchers), is an emerging example with the goal of completing this cycle of quality.

Recent experiences provide a sense of the exciting potential for adding value when a new research tool can be added to an existing data repository of colon cancer specimens. The resulting symbiotic collaboration discovered that only a small proportion (4%) of colon cancers failed to express a biomarker heralding a good prognosis. Importantly, the benefits of adjuvant chemotherapy were nearly all within this small biomarker-negative group, thus giving real meaning into precision medicine (12). There is also a countervailing need for caution about return on investment of data sharing, given the limited uptake by investigators to access data from over 500 available clinical trials, only a small minority of which reached publication status (13).

The ultimate landing for data sharing remains unclear, but its time has arrived, and all of us need to participate. The need for sharing transcends clinical trials and should reasonably extend to registries and population studies in this new era of big data. We need now to appropriately embrace it for our patients and other stakeholders.

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