Paradigms and perspectives

Clinical trial data access: Opening doors with TrialShare

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The need for improved access to clinical trial data is widely recognized to ensure complete information is in the public domain, to honor the commitment of research subjects, and to empower and engage analytic talent across the worldwide biomedical community. Open access to patient-level data from clinical trials enables data transparency, fosters data sharing, and catalyzes research innovation. As noted by Ross and Krumholzm[1] "A wall surrounds much… clinical research data, sequestering knowledge, impeding the free flow of information, and obscuring a clear view of the totality of evidence relevant to many research questions and clinical decisions." Mello et al[2] stress the benefits of data transparency, which range from improving reporting accuracy to improving patient safety, as well as speeding innovation.

Long-term benefits of data sharing include improvements in future clinical trial design, generation of new research hypotheses and research grant applications, and identification of targets for future drug development. Indeed, the National Institute on Drug Abuse Treatment Clinical Trials Network Data Share Project recently documented 13 published examples of secondary use of public data sets from National Institute on Drug Abuse–sponsored clinical trials,[3] illustrating the potential to promote additional research and new insights from completed studies.

Immune Tolerance Network (ITN) TrialShare, a novel portal for viewing and analyzing complete data sets from ITN trials, demonstrates this commitment through open access and user-friendly analytic tools. ITN TrialShare integrates data display from laboratory outputs, biomarker outcomes, and clinical and demographic attributes across a wide range of immunologic diseases and interventions, including the recent Learning Early About Peanut Allergy (LEAP) and LEAP-ON studies. This has enabled interested investigators to directly access and use large data sets for novel discovery and/or validation purposes, lowering many common barriers in translational research. In this brief article we describe our early experience with TrialShare, an online research resource that provides immunologic and clinical trial data from the ITN.

Central to the concept of responsible sharing of clinical trial data are the principles that trial participants, the public, research sponsors, and the research community are collective stakeholders in the clinical trial enterprise and that future research advances and the public trust are best served by access to complete data sets that emerge from such trials.[1] Support for this principle, although widespread, is often tempered by barriers to implementation, including concerns about patient confidentiality, risks of biased or flawed reanalysis, potential loss of competitive advantage, accountability of data generators and users, and high anticipated costs of data-sharing infrastructure.[2,4] In contrast, TrialShare is open to all interested parties without imposing limitations or conditions on access and was designed to ensure data transparency that will expand use of data sets for the public good.

The ITN is a National Institute of Allergy and Infectious Diseases/National Institutes of Health–sponsored academic clinical trial network that designs, conducts, and reports clinical research and clinical trials involving immunologic therapeutics for allergy, autoimmunity, and transplantation tolerance. TrialShare (www.itntrialshare.org) was conceived to facilitate wide access for interested parties to data, samples, and specialized tools for visualization, discovery research, and reanalysis. The TrialShare portal, which was released for public access in August 2013, provides complete open access to clinical trial data and laboratory studies from ITN trials at the time of the primary study publication. Currently, data from 20 clinical trials are available to the public, including the recent peanut allergy prevention studies called LEAP and LEAP-ON,[5,6] and data from an additional 17 clinical trials are posted on the internal TrialShare site and will be released to the public at the time of first publication. ITN TrialShare is now also being linked to publications from other National Institute of Allergy and Infectious Diseases–sponsored clinical research consortia.[7,8] Recently, the ITN TrialShare portal received the first National Academy of Sciences Data and Information Challenge award, which was established by the Academy's Board on Research Data and Information under the theme "Using data for the public good."

A key principle and operational feature of TrialShare is that public access is unfettered. Each user provides only an E-mail address and password to establish an account. On logging in, users have access to clinical trial protocols; case report forms; complete trial results; extensive deidentified participant-level data, including a variety of immunology laboratory outputs; visualization tools; user-defined filtered report views; and statistical analysis codes, with the option to create alternate analyses and

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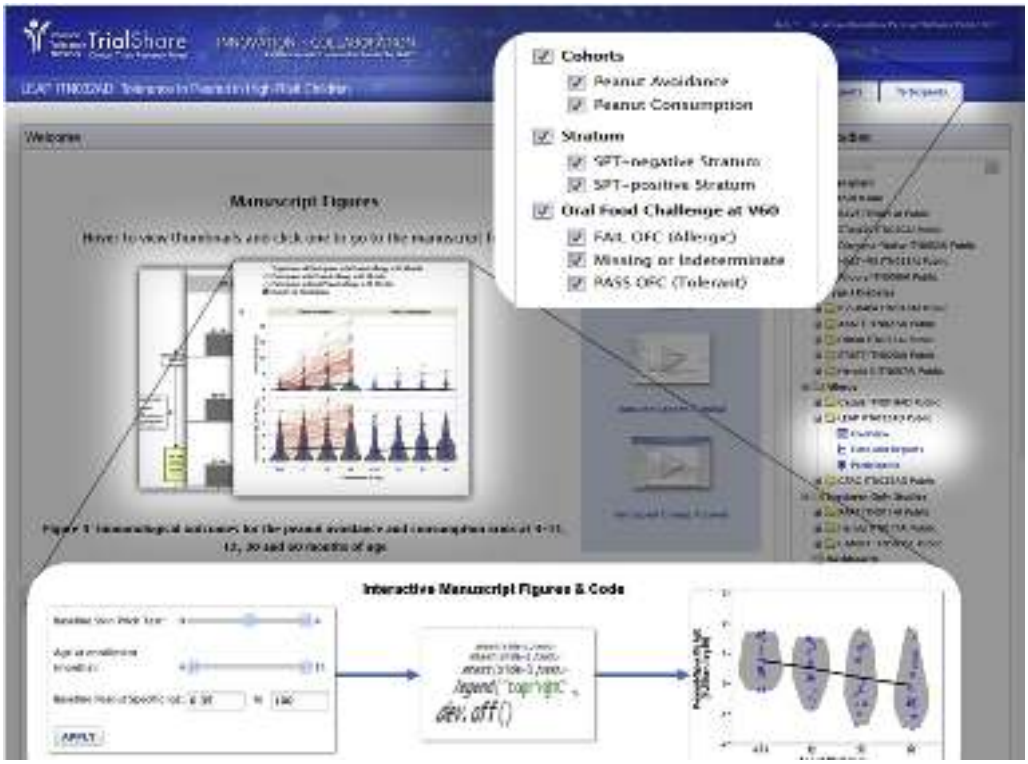

FIG 1. Interactive TrialShare data display for the ITN LEAP trial in peanut allergy.[5] Users can select published figures *(upper left)* and reanalyze the data that are represented by using user-defined subsets of participants or laboratory criteria *(upper right)*. An interactive "slider" bar is provided *(lower left)* to enable easy assessment of different data cutoffs, with real-time plotting of the data using these user-defined reanalysis criteria *(lower right)*. This plot highlights an example of uncovering decreasing IgE titers to peanut allergen in subjects with high initial skin prick test reactivity, a finding not evident in the published figure, which showed aggregated data from all subjects. Access to ITN clinical trial data is available at www.ITNTrialshare.org.

the ability to download data sets for offline use within a user's own domain. In this regard TrialShare goes beyond alternative data-sharing models to encourage reuse and reanalysis of data and might facilitate future use in currently unforeseen ways. TrialShare was designed to accelerate exploration of secondary research questions, enable alternative analyses and conclusions, and promote development of new conceptual models. Examples of user interfaces illustrating some of these parameters are shown in Fig 1.[5]

TrialShare users can also access a searchable database of the ITN biospecimen repository and download forms to request samples. Direct Web links to TrialShare are embedded in the Methods sections, figure legends, or both of online publications resulting from each trial and are also included in the trial listing at www.ClinicalTrials.gov. In the interest of fostering insightful peer review, the ITN has provided anonymous TrialShare access to journal peer reviewers, statisticians, and editors at the time of manuscript submission.

External users of TrialShare (unaffiliated with the ITN) have access to clinical outcome data, together with clinical and laboratory parameters that include standard CBC and chemistry panels; flow cytometry; and measurement of serum cytokine and chemokine levels, gene expression, antigen-specific B- and T-cell responses, and clonality of immune responses as determined by T- and B-cell receptor sequencing; and high-resolution immunohistopathology images, with 30 to 100 unique users accessing 1,000 to 3,000 page views each month (Fig 2). Online tools allow reanalysis of study assays, including more than 10,000 specific antibody tests and nearly 4,000 flow cytometric files from more than 1,000 study participants. More than 1,300 ITN TrialShare data sets have been downloaded by public users to their local computer networks for customized analyses. The TrialShare application interface allows rapid searching of study data and associated manuscripts for those not familiar with ITN studies along with tools for interactive reanalysis of the published data. External users who plan to publish secondary analyses using TrialShare data must acknowledge the original source of data and are encouraged, although not required, to contact ITN for discussions to help ensure accuracy of these reports. Collectively, these capabilities and applications of TrialShare go beyond those described for other data-sharing platforms and might account for the relatively high TrialShare use to date.

Our experience is indicative of broad interest spanning diverse scientific and medical communities. Use over the 24 months since TrialShare's introduction is distributed across academic (.edu), nonprofit (.org), government (.gov), and corporate (.com) users. In addition, subjects using "unaffiliated" domains (eg, Gmail and Yahoo) constitute a substantial number of logins to TrialShare, likely representing journal readers or others without the above affiliations. Internal ITN users (ie, study teams, manuscript writing groups, investigators, and biostatisticians) use the TrialShare interface as the primary mechanism for data aggregation, analysis, presentation, and manuscript development in all ITN trials.

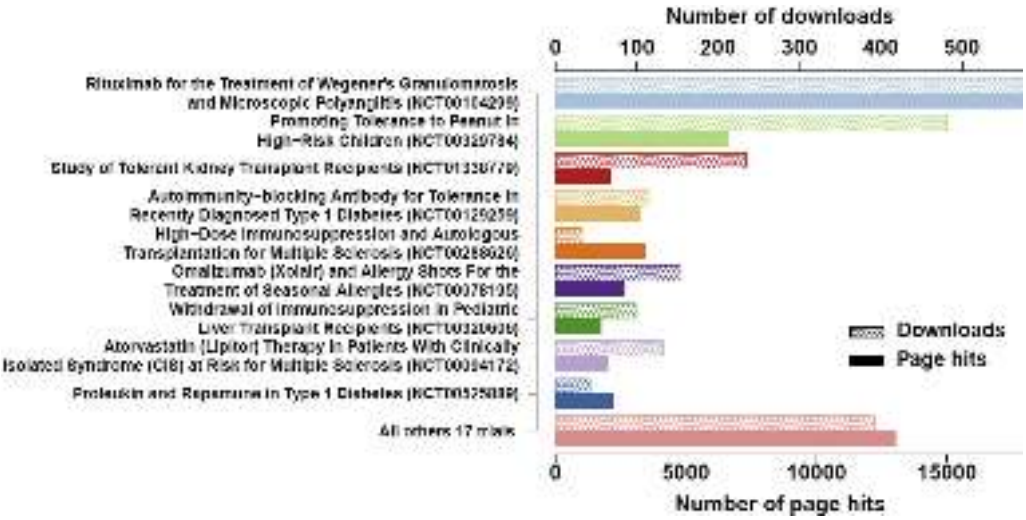

FIG 2. Public access activity for ITN clinical trials with data and associated analyses available on TrialShare (itntrialshare.org). Web page views are shown with *solid bars* scaled to the *bottom axis,* and data set/report downloads are shown with *hatched bars* scaled to the *top axis.* Activity through the first 18 months of TrialShare open access is shown.

Alternative data-sharing projects, such as the Yale Open Data Access Project and the Clinical Studies Data Access Project embody many similar goals, but each of these uses an independent learned intermediary to (1) review and approve requests for data access; (2) assess the qualifications of data requestors to conduct their proposed analyses; and (3) seek preaccess commitment to analytic and publication plans. Other features might include negotiation of data-use agreements and provisions to protect the competitive advantage of primary data generators. These stipulations are significant barriers to broad use, and we believe that the need for such precautions should be balanced against the value of truly open access without potentially burdensome preconditions. Indeed, although some investigators were initially concerned about potential loss of attribution or improper use of "their" data, such issues have not materialized and are more than offset by the value of encouraging thorough data dialogues at the time of original publication. Several National Institutes of Health institutes provide access to final data sets from National Institutes of Health–sponsored clinical trials but generally do not provide tools for data visualization or reanalysis, and user agreements and registration requirements vary.

The costs of data sharing and how those costs are borne by research sponsors, data generators, users, and other stakeholders are important topics. Although only limited information on such costs are available, estimates of such costs have ranged as high as 10% to 15% of the costs of a given clinical study.[9] The ITN provides dedicated resources, including data and biostatistical support staff, who transform and enter data from established outputs at each site or laboratory for loading into the TrialShare system, along with training, maintenance, hardware, and computational support that minimizes the effort typically required of individual investigators who wish to share their data. After the initial investment in 2013-2014 (approximately 5% of concurrent ITN expenditures), the ongoing human resource, operational, computational, and infrastructure maintenance costs are modest, amounting to approximately 0.5% to 2% of the total cost of a clinical trial. Thus our experience to date suggests that costs should not be a significant barrier to data sharing for many research sponsors. However, we recognize that aspects of TrialShare staffing, methodology, and other features are unique and might preclude broad generalizations. Of note with regard to cost considerations, TrialShare is built on an open source framework (LabKey Server, www.labkey.org) that has served as a model for more than 40 collaborative workspaces developed by other government, industry, nonprofit, and academia-sponsored consortia; in addition, we use an open source statistical program for analytics to encourage independent validation and secondary use.

We encourage the use of ITN TrialShare by the biomedical community and offer our early experience as a positive indicator of interest and appropriate use, fostering independent analyses and honoring the commitment of participants and the public to clinical trials through open access to data from these trials.

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