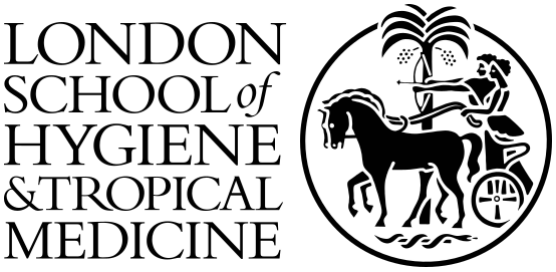

Academic Research Organization Consortium for Continuing Evaluat; Patel, MR; Armstrong, PW; Bhatt, DL; Braunwald, E; Camm, AJ; Fox, KA; Harrington, RA; Hiatt, WR; James, SK; +320 more... Kirtane, AJ; Leon, MB; Lincoff, AM; Mahaffey, KW; Mauri, L; Mehran, R; Mehta, SR; Montalescot, G; Nicholls, SJ; Perkovic, V; Peterson, ED; Pocock, SJ; Roe, MT; Sabatine, MS; Sekeres, M; Solomon, SD; Steg, G; Stone, GW; Van de Werf, F; Wallentin, L; White, HD; Gibson, M; , COLLABORATORS; Patel, MR; Armstrong, PW; Bhatt, DL; Braunwald, E; Camm, A; Fox, KA; Harrington, RA; Hiatt, WR; James, SK; Kirtane, AJ; Leon, MB; Lincoff, A; Mahaffey, KW; Mauri, L; Mehran, R; Mehta, SR; Montalescot, G; Nicholls, SJ; Perkovic, V; Peterson, ED; Pocock, SJ; Roe, MT; Sabatine, MS; Sekeres, M; Solomon, SD; Steg, G; Stone, GW; Van de Werf, F; Wallentin, L; White, HD; Gibson, C; Achaval-Giraud, A; Aguilar Salinas, CA; Alexander, JH; Almeida, ED; Ambrosio, G; Ann, R; Annichino-Bizzacchi, JM; Antman, E; Antonescu, A; Antorrena-Miranda, I; Apartsin, K; Arce, M; Arellano-Rodrigo, E; Assadourian, A; Astrahanceva, A; Badings, E; Bainey, KR; Banik, M; Belisário Falchetto, E; Berrospi, P; Bezrodna, L; Bianco, HT; Blikhar, O; Blokhin, A; Bobade, M; Bohula, E; Booth, DC; Botta, CE; Bozkurt, ED; Bradley, C; Brito, M; Brugaletta, S; Burmak, LG; Button, A; Bylova, N; Byrne, J; Calin, P; Carrión, AM; Célia Corrêa e Castro Marinho, M; Celic, V; Cerci, RJ; Cervantes Hurtado, A; Cherkezov, E; Chopskie, E; Conrado, Y; Crisan, C; Cuervo, A; Dattani, ID; de los Ríos Ibarra, MO; de Padua Mansur, A; de Souza Pantano, G; Del Razo-Olvera, F; Delia, M; Dellborg, M; Dias, C; Díaz Díaz, JL; Dimov, B; Dolzhenko, M; Dominguez Simeon, MJ; Dumitrascu, A; El Din El Shafey, W; El Jarroudi, F; Estrada, RI; Evans, S; Ezekowitz, J; Ferkl, R; Fil, W; Fimiani, F; Finfer, S; Flecknoe-Brown, S; Forero Gómez, JE; Fresco, C; Galatius, S; Gandur, H; Garcia, B; Garcia, L; Garcia Alvarez, JA; García-Hernández, PA; Garvey, M; Georgiev, B; Gibson, CM; Gibson, A; Giugliano, RP; Godoy Palomino, AL; Goloborodko, B; Goloshchekin, B; González Castaño, M; González Martínez, FJ; GonzalezColaso, P; Goodman, S; Gupta, S; Hajko, E; Hall, R; Hamilton, M; Hammond, N; Hansen, O; Henderson, RB; Hernandez, A; Hovingh, GK; Hueb, W; Husted, S; Igor, A; Irina, M; Jambaulikar, G; Jimeno, CA; Johansson, Å; Johnson, B; Karlsson, JE; Kastelein, J; Kinoshita, C; Klausner, HA; Koura, F; Koval, O; Krievins, D; Kuehl, A; Kulyk, A; Kunecki, M; Kutsogiannis, DJ; Lakatos, F; Lareva, N; Lassila, R; Legkonogov, A; Lema, J; Lema, J; Lenka, R; Lewis, B; Lip, GY; Łukaszewicz, M; Lypovetska, S; Macchiavelli, AJ; Mader, P; Mafrici, A; Maguire, H; Maia, LN; Malygin, A; Malynovsky, Y; Mani, A; Manyari, D; Margoczy, R; Marino, M; Martin-Loeches, I; Martin-Loeches, I; Matteo, M; McCollum, C; Meelu, OA; Mehran, R; Melendez, G; Meseguer, ML; Minarik, P; Minhas, E; Misik, KK; Misir, M; Montalescot, G; Monteagudo Canto, A; Montecinos, H; Morales, A; Mot, S; Mottershead, J; Murakami, K; Myronenko, S; Myśliwiec, BJ; Nadbrzezny, P; Nicholls, S; Nikolsky, E; O'Connor, M; Obaitan, I; O'Donoghue, M; Ohman, EM; Omerovic, E; Osborne, J; Oyesile, B; Parliteanu, O; Pavelko, M; Peacock, WF; Penzes, J; Pham, DN; Pilgrim, T; Piskorz, D; Pollak, A; Ponce, G; Popescu, M; Prokop, D; Prostov, I; Quadros, A; Raev, D; Rafalskiy, V; Rastogi, P; Real, V; Resnick, M; Ribas Fortes, JA; Riding, D; Rincón, LM; Riojas,

portunity to conduct confirmatory analyses before publication of an article, thereby advancing the ICMJE's stated goal of increasing "confidence and trust in the conclusions drawn from clinical trials." Finally, persons who were not involved in an investigator-initiated trial but want access to the data should financially compensate the original investigators for their efforts and investments in the trial and the costs of making the data available.

The writing committee of the International Consortium of Investigators for Fairness in Trial Data Sharing included P.J. Devereaux, M.D., Ph.D., Gordon Guyatt, M.D., Hertzel Gerstein, M.D., Stuart Connolly, M.D., and Salim Yusuf, M.B., B.S., D.Phil. — all from McMaster University, Hamilton, ON, Canada. This article was reviewed and endorsed by 282 investigators in 33 countries, who are listed in the Supplementary Appendix.

Disclosure forms provided by the authors are available at NEJM.org.

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Sharing Data from Cardiovascular Clinical Trials — A Proposal

The Academic Research Organization Consortium for Continuing Evaluation of Scientific Studies — Cardiovascular (ACCESS CV)

Participants in clinical research volunteer in order to support the development of scientific knowledge and help future patients. Inherent in their commitment is the belief that research will lead to new insights that will be disseminated. As clinical researchers, we fully support the concept of data sharing as fundamental to achieving this goal.

We formed the Academic Research Organization Consortium for Continuing Evaluation of Scientific Studies — Cardiovascular (ACCESS CV) to provide avenues for sharing data from cardiovascular clinical trials while minimizing risks and unintended consequences. The goal of the consortium is to create a strategy to thoughtfully operationalize the recommendations of the International Committee of Medical Journal Editors (ICMJE) and the Institute of Medicine (IOM) for sharing clinical trial data.[1,2] The ACCESS CV partners broadly support the concepts of data transparency and open access. The benefits of sharing patient-level data from clinical trials include confirmation of results, opportunities for new discoveries from secondary analyses, and eventually the possibility of aggregation of data sets from related studies to facilitate high-quality systematic meta-analyses.

The potential benefits of sharing patient-level data need to be balanced against potentially unintended consequences (see the Supplementary Appendix, available with the full text of this article at NEJM.org). We have identified the following challenges: complexity of the data and metadata, publication bias or selection bias in proposed new analyses, increased risk of type I error (from multiple unplanned secondary analyses), and patient privacy.

Clinical trial databases are commonly large and complex, often containing millions of data points from various sources (e.g., case-report forms, central laboratory review, safety reporting, and end-point adjudication). Attempts to validate trial findings made by persons who are either unfamiliar with the data set structure or inexperienced in the analysis techniques could create apparent discrepancies where none exist, potentially alarming the public and hindering rather than advancing science. The problem may be compounded by publication bias, which may lead to undue focus on findings that seem to differ from those of the original analysis.

In addition, data sharing could lead to a large number of unrestricted and non–hypothesis-driven supplementary data analyses, which would increase the risk of finding false associations (type I errors). Unplanned exploratory analyses from a publicly shared database may be numerous and redundant. The lack of adjustment for multiple testing and the absence of prespecified hypotheses and transparent analytic plans could result in spurious findings, which might obscure the real evidence.

Another potential hazard of

sharing individual-patient–level data is loss of patient privacy. Most patients in a deidentified database can be identified on the basis of their birth date, sex, and ZIP Code.[3] Those with rare diseases and the very elderly are at an even higher risk of identification and privacy violation.

We propose a secure method of sharing sensitive patient data that balances the legitimate desire of the scientific community for data access with the responsibility to ensure high-quality analyses and protection of patients' expectation of privacy.

First, with regard to governance of access to trial data, we propose that after publication of the primary results of a trial, researchers who were not involved with the trial design or conduct may send requests for analyses to the trial's publications committee. Beginning 24 months after publication, analysis requests should be considered by a learned review group comprising ACCESS CV members who were not involved in the trial, along with the trial's principal investigator, a trial statistician, and a member of the data and safety monitoring board. The 24-month period was chosen to allow time to build secure access to the database and to allow trial investigators to perform their own preplanned secondary analyses. The group's responsibility would be to review all proposals and approve those that are feasible, hypothesis-based, nonduplicative, and guided by investigators with technical capability and a plan for publication. All requests and subsequent decisions would be posted on an ACCESS CV Web portal, ideally within 60 days.

Second, we contend that it is critical to facilitate access in an orderly manner to support the best science and minimize patient risk. We envision the following elements of a mechanism of access to ensure a systematic approach: standardized requests on a Web portal, disclosure of conflicts of interest and publication plans, adherence to data-use agreements for planned analyses, provision of appropriate ethics approval, performance of all analyses using a secure Web link with an accompanying audit trail, and notification about submission for publication.

Such a process would avert the problem of multiple groups proposing the same analysis and would require investigators to have prespecified analysis plans. The ICMJE and the IOM[3] have stated that data-sharing plans should be provided at the time of trial registration and that the results from a clinical trial should be published in a timely fashion, with individual patient data available 6 months after publication. The IOM recommends full database access for secondary analyses beginning 18 months after trial completion. (For our specific responses to these recommendations, see the Supplementary Appendix, available at NEJM.org.)

We propose the following: ACCESS CV members would post data-sharing plans, following the ACCESS CV proposal, on ClinicalTrials.gov. Briefly, starting at the time of publication of primary trial results, secondary-analysis requests from researchers not involved in the trial would be submitted to the trial publications committee. When needed, ACCESS CV would provide a mechanism for validating the primary results using the individual patient data underlying the primary publication of a clinical trial, no later than 12 months after publication. Starting 24 months after the publication of primary results, requests for data access for secondary analyses would be promptly reviewed by a learned review group, as described above. ACCESS CV plans to build a Web-based portal that allows for the public posting of all data requests and the subsequent decisions of the independent review panel.

An unresolved issue is the question of how to provide meaningful academic credit (typically authorship) to the team that designed and conducted the trial, given that trials are usually enormous undertakings requiring several years of work. During the review of proposals for secondary analyses, we would expect trial leaders and people requesting access to data to consider and discuss this important issue and to reach consensus on a path forward for each analysis.

ACCESS CV recognizes that to achieve these goals, adequate resources and funding are required. Since that significant matter has not been addressed, we plan to work with sponsors of clinical trials, the IOM, the ICMJE, governmental bodies, and regulatory authorities to develop the infrastructure for the data-sharing proposal we describe.

ACCESS CV fully supports transparency and open data sharing. We propose these mechanisms for structured data access in an effort to provide ready access to trial data in a timely manner while minimizing risks

and barriers. We believe that ACCESS CV is well positioned to generate and share clinical trial data and, eventually, to develop aggregate data sets in cardiovascular medicine (see the Supplementary Appendix). The current proposal, though specific to cardiovascular clinical trials, may apply equally to other disciplines in which groups may consider building consortia and similar strategies. We aim to increase the utilization of shared data as compared with ongoing open-access efforts.[4,5] We believe our plans are aligned with the IOM's recommendations and with the ICMJE proposal and that they will ultimately maximize the impact of clinical trials on human health around the world.

The authors, who are initial partners in ACCESS CV, are Manesh R. Patel, M.D., Paul W. Armstrong, M.D., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., A. John Camm, M.D., Keith A.A. Fox, M.B., Ch.B., Robert A. Harrington, M.D., William R. Hiatt, M.D., Stefan K. James, M.D., Ph.D., Ajay J. Kirtane, M.D., Martin B. Leon, M.D., A. Michael Lincoff, M.D., Kenneth W. Mahaffey, M.D., Laura Mauri, M.D., Roxana Mehran, M.D., Shamir R. Mehta, M.D., Gilles Montalescot, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Eric D. Peterson, M.D., M.P.H., Stuart J. Pocock, Ph.D., Matthew T. Roe, M.D., M.H.S., Marc S. Sabatine, M.D., M.P.H., Mikkael Sekeres, M.D., Scott D. Solomon, M.D., Ph.D., Gabriel Steg, M.D., Gregg W. Stone, M.D., Frans Van de Werf, M.D., Ph.D., Lars Wallentin, M.D., Ph.D., Harvey D. White, D.Sc., and C. Michael Gibson, M.D. The institutional affiliations of the partners and the full list of ACCESS CV participants are provided in the Supplementary Appendix, available at NEJM.org.

Disclosure forms provided by the authors are available at NEJM.org.

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