

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Swedberg, K; Borer, JS; Pitt, B; Pocock, S; Rouleau, J; (2016) Challenges to Data Monitoring Committees When Regulatory Authorities Intervene. *The New England journal of medicine*, 374 (16). pp. 1580-4. ISSN 0028-4793 DOI: <https://doi.org/10.1056/NEJMsb1601674>

Downloaded from: <http://researchonline.lshtm.ac.uk/2535716/>

DOI: <https://doi.org/10.1056/NEJMsb1601674>

Usage Guidelines:

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: Copyright the publishers

<https://researchonline.lshtm.ac.uk>

SOUNDING BOARD

Challenges to Data Monitoring Committees When Regulatory Authorities Intervene

Karl Swedberg, M.D., Ph.D., Jeffrey S. Borer, M.D., Bertram Pitt, M.D., Stuart Pocock, Ph.D., and Jean Rouleau, M.D.

New pharmaceutical agents are best evaluated in randomized, controlled clinical trials in which both the safety of participants and the adequacy of conduct are monitored by an independent data monitoring committee as described in reports from regulatory organizations.¹⁻³ A data monitoring committee can recommend discontinuation of a trial because of futility or because of overwhelming benefit or unacceptable harm associated with an agent, and it can recommend modification of a trial for safety. The data monitoring committee should review relevant contributory information from parallel studies⁴⁻⁸ in order to make appropriate recommendations.

Regulatory authorities also must evaluate trial data, but they should not interfere in the conduct of the trial if an independent data monitoring committee determines that the progress of the trial is appropriate and no modification is required for safety. Here we report our recent experience with a regulatory action that we consider to be a threat to the function of data monitoring committees and potentially to the integrity of monitored trials.

The renin inhibitor aliskiren was approved for use in patients with hypertension in the United States in 2005 and in the European Union in 2007. We were the data monitoring committee for both the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT), which evaluated the effects of aliskiren in addition to an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) in patients with acute heart failure,⁹ and the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE), which compared three treatments (enalapril, aliskiren, and a combination of these two agents) in patients with chronic heart failure.¹⁰

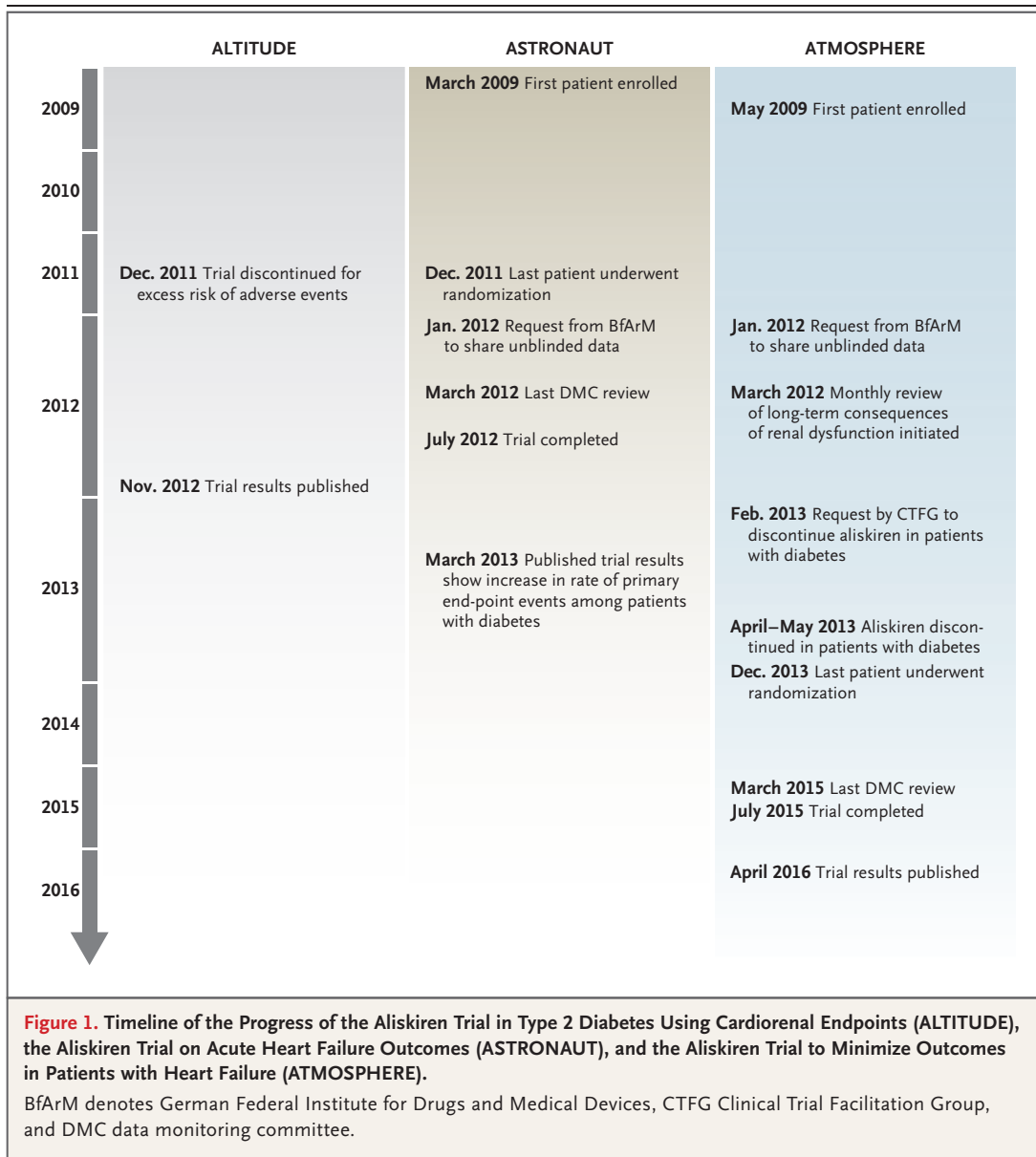
In December 2011, when recruitment to

ASTRONAUT was closed, a third trial, the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE), was terminated because the excess risk of adverse events with aliskiren outweighed any potential benefits (Fig. 1). At the time, 69% of the projected events had occurred.¹¹ ALTITUDE was conducted in patients with type 2 diabetes and chronic kidney disease, chronic cardiovascular disease, or both; like ASTRONAUT, it evaluated aliskiren in addition to either an ACE or an ARB.

The ALTITUDE findings raised concern about the potential for adverse effects of aliskiren in other trials, especially in patients with diabetes. In January 2012, the German Federal Institute for Drugs and Medical Devices (BfArM) asked the chair of the data monitoring committee about the effects of aliskiren in patients with diabetes in the two trials we monitored.

At the time of the BfArM inquiry, the most recent safety report of the ASTRONAUT data monitoring committee, from December 2011, included 1430 patients who had undergone randomization (89% of the projected total), of whom 42% had diabetes. The average follow-up was 7 months. In patients with diabetes, renal dysfunction had developed in 14.1% of the patients receiving aliskiren, as compared with 10.2% receiving placebo. The trial results were neutral with respect to the primary end point (death from cardiovascular causes or rehospitalization within 6 months), but only two thirds of the reported events had been adjudicated.

We reassured the BfArM that the ALTITUDE findings would be considered in our recommendations for trial conduct in ASTRONAUT. To maintain the integrity of the trial, however, we would not release the ASTRONAUT data we were monitoring. At our March 2012 review, the December pattern of events persisted, so we recom-



mended continuation of the trial to its planned completion 4 months later. When the results of ASTRONAUT were published,¹¹ among 20 subgroups analyzed, there was a significant increase in the rate of primary end-point events with aliskiren, as compared with placebo, among patients with diabetes at 12 months, but not at 6 months, and there was a significant reduction in this rate among patients who did not have diabetes.¹²

The December 2011 safety report of the ATMOSPHERE data monitoring committee included 5441 patients, of whom 1581 had diabetes.

In the combination-therapy group, patients with diabetes had significantly more renal dysfunction and hyperkalemia than did patients without diabetes, and these conditions were associated with a higher rate of primary-composite-outcome events (deaths from cardiovascular causes or hospitalizations for heart failure). However, these events were relatively infrequent, and there were slightly fewer primary composite events in the combination-therapy group than in either of the single-therapy groups both in patients with diabetes and in those without diabetes.

After the BfArM inquiry, we again reviewed

ATMOSPHERE 4 months later, taking into account both the ALTITUDE and the ASTRONAUT results. We found no change in patterns of events and no reason to alter the trial. We also investigated whether patients with renal dysfunction (both in patients with diabetes and in those without diabetes) had any excess of adverse clinical outcomes, including deaths from non-cardiovascular causes. These results were updated monthly and provided to the chair of the data monitoring committee. No excess of adverse outcomes was found.

In February 2012, the ATMOSPHERE data monitoring committee recommended continuation of the trial despite the ALTITUDE results; this recommendation was accepted by the executive committee of the trial. In April 2012, BfArM requested more frequent safety reviews by the data monitoring committee than the number of reviews mandated by the trial protocol and charter. The data monitoring committee had already increased the frequency of reviews; was monitoring patients with diabetes, renal dysfunction, or both with more detailed analyses; and found that the previously observed differences in the consequences of renal events among the treatment groups had disappeared. No new concerns were identified and, in the overall population, the effects on the primary outcome continued to be numerically lowest in the combination-therapy group.

The January 2013 review of 6381 randomly assigned patients in ATMOSPHERE further reassured the data monitoring committee of the overall safety of combination therapy, since no new safety issues were identified. There were numerically fewer hospitalizations for heart failure, deaths from cardiovascular causes, myocardial infarctions, and strokes with combination therapy than with enalapril alone, and there was a significant benefit of combination therapy with respect to the primary end point. Our unanimous recommendation to the sponsor and executive committee was to continue ATMOSPHERE according to the protocol.

In February 2013, on the basis of data from ALTITUDE and ASTRONAUT, but without knowledge of the unblinded ATMOSPHERE results, the Clinical Trial Facilitation Group of the European Union requested that the sponsor of ATMOSPHERE, Novartis, discontinue administration of aliskiren in all patients with diabetes in

ATMOSPHERE. The data monitoring committee had already informed BfArM that it had considered the results of ALTITUDE and ASTRONAUT when recommending that ATMOSPHERE continue as planned and was conducting careful analyses regarding patients with diabetes. The sponsor and executive committee expressed confidence in the data monitoring committee. However, in accordance with the mandate of the Clinical Trial Facilitation Group, administration of aliskiren was discontinued in patients with diabetes in April and May 2013 and follow-up data on these patients were censored at the time of discontinuation of aliskiren. This resulted in the need to prolong ATMOSPHERE by 1 year to meet event targets.

In March 2015, when randomization was complete, the data monitoring committee conducted its last data review and recommended continuation of the trial to its planned ending in July 2015. The article by McMurray et al. now published in the *Journal* reports the final trial results.¹³ The report indicates that there was no significant difference in the primary trial outcome or in the outcome of death from any cause among the three trial groups. There was also no evidence of a differential effect of aliskiren or of combination therapy in patients with diabetes as compared with those without diabetes.

Concerns regarding the effect of reported external evidence on interventions evaluated in ongoing clinical trials have been well documented.^{5,8} When the strength of external evidence is indisputable and the pathophysiologic processes are similar to those in the ongoing trial, the impact of these findings generally should be immediate, with a prompt change in the trial protocol to reflect the concerns raised. If the strength and relevance of the external data are less decisive, reliance on the judgment of the data monitoring committee is appropriate, since it is this committee that is tasked with considering the totality of evidence in monitoring the ongoing trial.

Given the results of ALTITUDE and ASTRONAUT, the concerns of the regulators regarding patients in ATMOSPHERE were reasonable. However, it is noteworthy that ATMOSPHERE had a run-in period that helped to identify patients who could not receive enalapril or aliskiren without unacceptable adverse events; these patients then were excluded from randomization and long-term treatment. ALTITUDE and

ASTRONAUT had no such run-in period. Another potential contributor to the differences found is the patient population studied, since dual renin-angiotensin system blockade has not been shown to produce an additional benefit over single blockade in patients without heart failure,¹⁴ but it may be useful in patients with heart failure.¹⁵ In addition, multiple interventions that have proved to be of benefit in patients with chronic heart failure have not been beneficial in patients with acute heart failure.

In the future, we recommend that regulators consider the following course of action before requesting discontinuation of a study drug in patients in an ongoing trial as a result of emerging data from other trials. Regulators could request special attention to particular populations, such as those with diabetes in ATMOSPHERE, and request that the analysis plan of the data monitoring committee be extended. The data monitoring committee's statistical analysis plan to deal with such concerns could be shared with regulators to reassure them that the safety of potentially vulnerable patients is being properly assessed. The provision of this plan could be combined with a formal written statement from the data monitoring committee to the regulators after each meeting of the data monitoring committee; this statement would reiterate that the trial should continue as planned. Whether patients should be asked to provide additional informed consent after being informed of the new external evidence would depend on the strength and applicability of the evidence.

The course of action proposed by BfArM — that the data monitoring committee share unblinded data from ATMOSPHERE with the agency — is problematic. It could compromise the integrity of the trial, particularly if regulators in each country made the same request, thereby causing wider release of unblinded data. Sharing of unblinded data from ongoing blinded trials with several regulators could lead to a variety of interpretations, with consequent confusion about what appropriate measures should be taken to ensure patient safety.

We strongly recommend that the data monitoring committee in a clinical trial be allowed to act independently during the progress of the trial. If legitimate concerns arise regarding the safety of any intervention, as was the case here, sharing of data with regulators should be avoided.

In special cases, the data monitoring committee's statistical analysis plan to deal with these concerns should be shared with the regulators. A collective trust in the key responsibilities of the data monitoring committee is essential. We note that the sponsor and the regulatory agencies involved have written letters of reply (now published in the *Journal*) in response to our concerns,^{16,17} and we appreciate their interest in supporting efforts to prevent future problems of this kind.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Martina Wibberg (Datamap, Freiburg, Germany) for statistical support during the ASTRONAUT and ATMOSPHERE trials.

From the Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (K.S.); the National Heart and Lung Institute, Imperial College London (K.S.) and the Department of Medical Statistics, London School of Hygiene and Tropical Medicine (S.P.) — both in London; the Division of Cardiovascular Medicine, Howard Gilman Institute for Heart Valve Disease and Schiavone Institute for Cardiovascular Translational Research, State University of New York Downstate Medical Center, New York (J.S.B.); the University of Michigan School of Medicine, Ann Arbor (B.P.); and the Institut de Cardiologie de Montréal, Université de Montréal, Montreal (J.R.).

This article was published on April 4, 2016, at NEJM.org.

1. Guideline on data monitoring committees. London: European Medicines Agency, 2005 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf).
2. Food and Drug Administration. Guidance for clinical trial sponsors: establishment and operation of clinical trial data monitoring committees. 2006 (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>).
3. National Institutes of Health. Draft guidelines for establishing and operating a data and safety monitoring board. 2002 (<https://www.drugabuse.gov/funding/clinical-research/draft-guidelines-establishing-operating-data-safety-monitoring-board>).
4. DeMets DL, Fleming TR, Rockhold F, et al. Liability issues for data monitoring committee members. *Clin Trials* 2004;1:525-31.
5. DeMets DL, Fost N, Powers M. An institutional review board dilemma: responsible for safety monitoring but not in control. *Clin Trials* 2006;3:142-8.
6. Pocock S, Wang D, Wilhelmsen L, Hennekens CH. The data monitoring experience in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2005;149:939-43.
7. Pocock S, Wilhelmsen L, Dickstein K, Francis G, Wittes J. The data monitoring experience in the MOXCON trial. *Eur Heart J* 2004;25:1974-8.
8. Borer JS, Gordon DJ, Geller NL. When should data and safety monitoring committees share interim results in cardiovascular trials? *JAMA* 2008;299:1710-2.
9. Gheorghide M, Böhm M, Greene SJ, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. *JAMA* 2013;309:1125-35.
10. Krum H, Massie B, Abraham WT, et al. Direct renin inhibi-

tion in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure (ATMOSPHERE) study. *Eur J Heart Fail* 2011;13:107-14.

11. Parving H-H, Brenner BM, McMurray JJV, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;367:2204-13.

12. Maggioni AP, Greene SJ, Fonarow GC, et al. Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure: insights from the ASTRONAUT trial. *Eur Heart J* 2013;34:3117-27.

13. McMurray JJV, Krum H, Abraham WT, et al. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. *N Engl J Med*. DOI: 10.1056/NEJMoa1514859

14. The ONTARGET Investigators. Telmisartan, ramipril, or both

in patients at high risk for vascular events. *N Engl J Med* 2008; 358:1547-59.

15. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362: 767-71.

16. Tougas G, Aftring RP. Novartis reply to the ATMOSPHERE data monitoring committee. *N Engl J Med*. DOI: 10.1056/NEJMc1603515

17. Salmonson T, Janssen H, Sudhop T, Stahl E. Regulatory reply to the ATMOSPHERE data monitoring committee. *N Engl J Med*. DOI: 10.1056/NEJMc1603514

DOI: 10.1056/NEJMs1601674

Copyright © 2016 Massachusetts Medical Society.