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Reply to "Planned Analyses of the REDUCE MRSA Trial"

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In response to the comment by Huang and Platt (1) on our previous report (2), we point out that the ethical principles of trial registration can be traced back to the Declaration of Helsinki and require that the results of research involving human subjects be publicly available (3). As aptly stated by Alastair Wood (3), "... basic principles of evidence-based practice require the analysis of all data on a given topic; the practice of publishing only some results, but not others, undermines our collective ability to make rational decisions about medical care." Reporting of data is regulated by section 801 of the FDA Amendments Act (3).

Publication bias is created if only studies with results in a single direction, usually positive, are published. Thus, trial registration serves as a mechanism to help ensure that all metric results are available to the public. Many journals will not publish unregistered clinical trials. Data regarding trial registration are available online at http://clinicaltrials.gov/.

The REDUCE MRSA study (4) had several changes in the recorded metrics more than 6 months after the study completion date (Fig. 1). Central-line-associated bloodstream infections and urinary methicillin-resistant *Staphylococcus aureus* (MRSA) cultures were deleted. The lead author has given assurances that these deletions were done prior to trial completion and before data analysis; thus, publication bias did not exist. The lead author also stated that these results will be published in the future. It would have been best not to have deleted the ClinicalTrials.gov metrics.

In addition, during the revision of the REDUCE MRSA study's metrics on the ClinicalTrials.gov website, the metric of "ICU-attributable all-pathogen bloodstream infection" was added. Such additions should be done with caution. For example, if the threshold for statistical significance is 1 in 20 and, hypothetically, if after a trial 20 items are looked at, by chance, 1 may be positive. Thus, the decision to report such events after a trial has commenced needs to be clearly identified in Materials and Methods.

We feel that if the practice of not reporting, eliminating, or adding metrics after trial initiation by researchers stating that they

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This is a response to a letter by Huang and Platt (doi:10.1128/AAC.02792-13).

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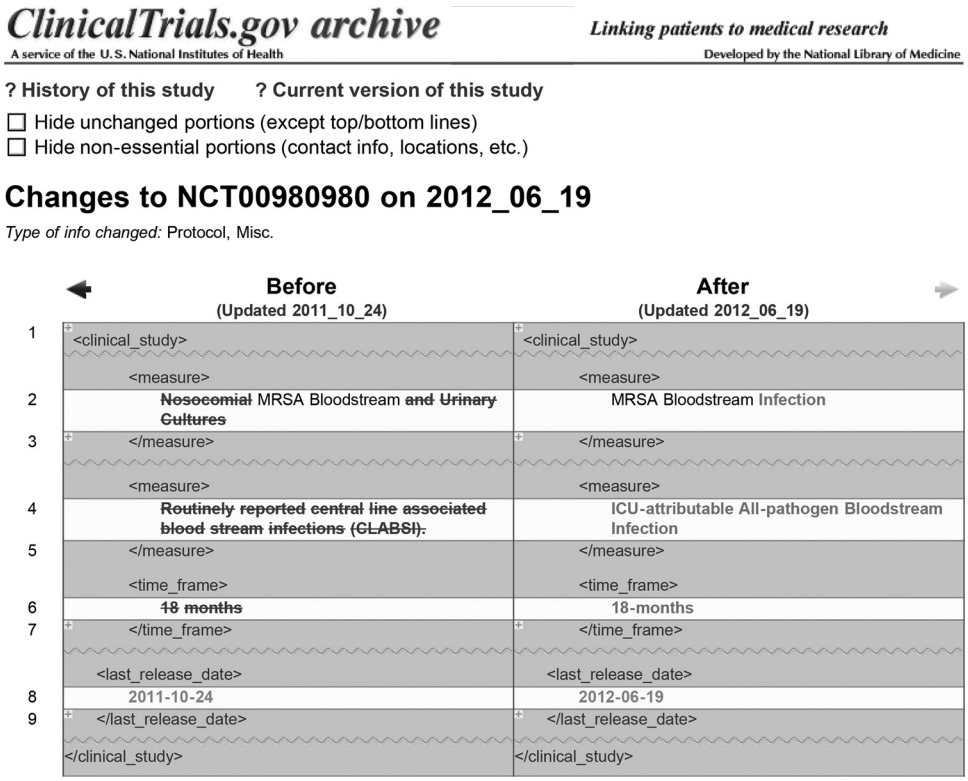

ClinicalTrials.gov archive
A service of the U.S. National Institutes of Health
Linking patients to medical research
Developed by the National Library of Medicine

? History of this study ? Current version of this study

☐ Hide unchanged portions (except top/bottom lines)
☐ Hide non-essential portions (contact info, locations, etc.)

Changes to NCT00980980 on 2012_06_19

Type of info changed: Protocol, Misc.

	Before (Updated 2011_10_24)	After (Updated 2012_06_19)
1	<clinical_study>	<clinical_study>
	<measure>	<measure>
2	~~Nosocomial~~ MRSA Bloodstream ~~and Urinary Cultures~~	MRSA Bloodstream Infection
3	</measure>	</measure>
	<measure>	<measure>
4	~~Routinely reported central line associated blood stream infections (CLABSI).~~	ICU-attributable All-pathogen Bloodstream Infection
5	</measure>	</measure>
	<time_frame>	<time_frame>
6	~~18 months~~	18-months
7	</time_frame>	</time_frame>
	<last_release_date>	<last_release_date>
8	2011-10-24	2012-06-19
9	</last_release_date>	</last_release_date>
	</clinical_study>	</clinical_study>

FIG 1 Changes in the REDUCE MRSA study recorded on 19 June 2012 on the ClinicalTrials.gov website after the September 2011 study completion and primary completion dates. (Reproduced from the ClinicalTrials.gov website.)

did not analyze or look at the data became widespread, the effectiveness and utility of trial registration would be negated and the system would become next to useless.

Having said that, we do believe that treating everyone may have short-term benefits. The study by Huang et al. is supported by the recent work of Derde et al. (5), who observed a significant decrease in MRSA infections with improved hand hygiene and unit-wide chlorhexidine decolonization protocols. There was not a significant decrease in vancomycin-resistant *Enterococcus* or *Enterobacteriaceae* isolates. The caveat to this approach is the possibility of the development of bacterial resistance, which may take over a decade to appear (6). Disturbingly, Derde et al. reported a 13 to 14% incidence of MRSA resistance to chlorhexidine (5). The wider effect on the microbiome of both the patient and the facility is unknown. But using protocols that indiscriminately and frequently cause mass destruction of bacteria should be done with caution. A better approach may be to use surveillance to target such interventions toward pathological bacteria while minimizing the effect on commensal and beneficial bacteria.

REFERENCES

1. **Huang SS, Platt R.** 2014. Planned analyses of the REDUCE MRSA trial. Antimicrob. Agents Chemother. **58:**2485. http://dx.doi.org/10.1128/AAC.02792-13.
2. **Kavanagh KT, Saman DM, Yu Y.** 2013. A perspective on how the United States fell behind Northern Europe in the battle against methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **57:**5789–5791. http://dx.doi.org/10.1128/AAC.01839-13.
3. **Wood AJ.** 2009 Progress and deficiencies in the registration of clinical trials. N. Engl. J. Med. **360:**824–830. http://dx.doi.org/10.1056/NEJMsr0806582.
4. **Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, Lankiewicz J, Gombosev A, Terpstra L, Hartford F, Hayden MK, Jernigan JA, Weinstein RA, Fraser VJ, Haffenreffer K, Cui E, Kaganov RE, Lolans K, Perlin JB, Platt R, CDC Prevention Epicenters Program, AHRQ DECIDE Network and Healthcare-Associated Infections Program.** 2013. Targeted versus universal decolonization to prevent ICU infection. N. Engl. J. Med. **368:**2255–2265. http://dx.doi.org/10.1056/NEJMoa1207290.
5. **Derde LP, Cooper BS, Goossens H, Malhotra-Kumar S, Willems RJ, Gniadkowski M, Hyrniewicz W, Empel J, Dautzenberg MJ, Annane D, Aragão I, Chalfine A, Dumpis U, Esteves F, Giamarellou H, Muzlovic I, Nardi G, Petrikkos GL, Tomic V, Martí AT, Stammet P, Brun-Buisson C, Bonten MJ, MOSAR WP3 Study Team.** 2014. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. Lancet Infect. Dis. **14:**31–39. http://dx.doi.org/10.1016/S1473-3099(13)70295-0.
6. **Center for Disease Dynamics, Economics & Policy.** 2013.First reported cases of bacterial resistance against key antibiotics. Center for Disease Dynamics, Economics & Policy, Washington, DC. http://cddep.org/tools/first_reported_cases_bacterial_resistance_against_key_antibiotics.