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Title

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Permalink

<https://escholarship.org/uc/item/21n4n2sn>

Journal

Clinical Pharmacology & Therapeutics, 111(1)

ISSN

0009-9236

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Publication Date

2022

DOI

10.1002/cpt.2256

Peer reviewed

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When are treatment blinding and treatment standardization necessary in real-world clinical trials?

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Relevant conflicts of Interest

Dr. Simon is an employee of Kaiser Permanente Washington. Dr. Horberg is an employee of Kaiser Permanente Mid-Atlantic. Dr. Califf is an employee of Verily Life Sciences and Google Health and is a Board member for Cytokinetics. All other authors declared no competing interests for this work.

Funding for this work

US Food and Drug Administration sponsored the “Examining the Impact of Real-World Evidence on Medical Product Development”. Dr. Simon was supported by the National Institute of Mental Health Cooperative Agreement U19MH092201. This information, content, and conclusions are those of the authors and should not be construed as the official position or policy of, nor should any endorsements be inferred by the U.S. government, The US Food and Drug Administration, or the National Academies of Sciences, Engineering.

ABSTRACT

Concerns regarding both the limited generalizability and the slow pace of traditional randomized trials have led to calls for greater use of real-world evidence (RWE) in the evaluation of new treatments or products. Real-world clinical trials or pragmatic trials often differ from traditional clinical trials in the use of open-label or nonblinded treatments delivered by real-world clinicians in community practice settings.

Blinding and standardization of treatment may sometimes be necessary for internal validity, but they may also obscure or distort meaningful differences between treatments. When investigators consider whether blinding of clinicians, patients, or assessors is necessary, we suggest they consider several specific questions: Will clinicians, patients, and assessors have expectations or preferences regarding benefits or adverse effects? How might those expectations affect treatment uptake, treatment adherence, or assessment of outcomes? Will expectations differ in the settings where trial results will be applied? How would blinding of treatment reduce biases? How would blinding obscure true differences between treatments? How would procedures necessary for blinding reduce acceptability or increase risk of trial participation? When investigators consider how strictly treatments should be standardized, we suggest they consider several specific questions: How would treatment effectiveness or safety vary according to clinician experience or expertise? What level of experience or expertise is available in potential trial settings and settings where trial results would be applied? Is some level of standardization necessary for valid inference? Considering any special vulnerabilities of the study population, is some level of standardization necessary to assure participant safety?

Introduction

While traditional randomized trials remain the gold standard for assessing efficacy and safety of novel treatments, the slow pace and uncertain generalizability of traditional trials have prompted a growing interest in real-world evidence (RWE), including pragmatic or real-world clinical trials conducted in community settings.¹⁻³ Recognizing the need both for more relevant evidence and a for more efficient evidence-generating process, the National Academies of Science, Engineering and Medicine Forum on Drug Discovery Development and Translation⁴ organized a series of workshops sponsored by the United States Food and Drug Administration focused on Examining the Impact of Real-World Evidence on Medical Product Development.⁵ Those workshops considered specific dimensions in which RWE studies might differ from traditional clinical trials: use of real-world data, less standardized treatment delivered by community providers, and assignment of treatments by some mechanism other than individual randomization. Expanding on these considerations, there are certain features that distinguish traditional clinical trials from real-world clinical trials or pragmatic trials. In traditional trials, study participant eligibility follows stringent criteria that restricts to patients likely to have the outcome of interest, likely to be responsive to the experimental intervention, and likely to adhere to treatment protocols. Conversely, pragmatic trials will include all participants with the condition of interest regardless of predicted risk, estimated responsiveness, or adherence likelihood. Traditional clinical trials apply meticulously specified experimental interventions with experienced practitioners in settings selected predicated on expertise with patients enrolled in the study. Pragmatic trials will include practitioners across the spectrum of usual care and in

the full range of clinical settings. While in traditional clinical trials, the comparison intervention will be narrowly defined and may include a placebo, pragmatic trials will use a comparison that resembles usual care or best alternative treatment approach.⁶

As participants in the aforementioned workshop series, we here discuss two questions prominent in those discussions: When is concealment or blinding of treatment assignment necessary? How strictly should treatment quality or intensity be standardized? Both questions involve “real-world” adaptations of traditional practice in clinical trials: open-label treatment and allowing natural variation in quality or intensity of treatment. For each of these questions, we identify specific issues that evidence generators should consider when designing real-world studies and that evidence consumers should consider when evaluating the validity and relevance of study results. These questions are most relevant to the design of pragmatic clinical trials, where investigators have some control over delivery of treatments and information available to study participants and personnel. But some of these questions may be relevant to design or interpretation of observational research.

Advantages and Disadvantages of Concealing or Blinding Treatment Allocation

The original impetus for blinding patients, clinicians, and outcome assessors in clinical trials was reducing bias due to expectations or preferences.⁷ Those preferences could influence clinicians’ delivery of treatments, participants’ adherence to treatments or reporting of outcomes, and assessors evaluations of

benefits or harms – all leading to systematic error. Potential biases introduced by unblinded or open-label treatment are most concerning when treatments are more complex or outcomes are more subjective. While pragmatic trials often evaluate treatments in common use, sample sizes in pragmatic trials are typically much larger than those in traditional randomized clinical trials conducted prior to initial approval. Consequently, unbiased detection of less common adverse effects may be an important secondary aim of some pragmatic trials.

Blinding or concealment, however, may adversely affect both the efficiency of evidence generation and the generalizability of the resulting evidence. In addition to any direct operational costs of delivering blinded treatments, blinding may significantly reduce enrollment, leading to both added expense and delay. The Estonian Postmenopausal Hormone Therapy Trial included comparisons of a woman's willingness to enroll for the non-blind and blind subtrials. The subject's overall willingness was increased if the woman was in the non-blind subtrial with a relative risk (RR) of willingness to enroll of 1.17 non-blind versus blind. Fewer exclusions in the non-blind arm, resulted in higher overall eligibility with a RR 1.10 non-blind vs blind. While similar numbers of patients met the first stage of eligibility and were randomized into the non-blind and blind subtrial (2087 and 2084, respectively), a larger proportion consented and were recruited in the non-blind arm (48.0% vs 37.4%).⁸ Procedures necessary for blinding or concealment may also influence decisions to enroll or distort the delivery of study treatments, reducing generalizability to real-world practice conditions. This is clearest, for example, when alternative treatments differ in their modes of delivery (oral vs. parenteral) or their requirements for clinical or laboratory monitoring. Requiring unnecessary

procedures to maintain blinding may obscure rather than reveal true differences between treatments in acceptability, adherence, and real-world effectiveness. In one of the few rigorous evaluations of the effects of blinding, the Estonian Postmenopausal Hormone Therapy trial⁸ included two parallel trial protocols, blinded and unblinded. The requirement for blinding both reduced the likelihood that potentially eligible participants would enroll and yielded a study population less representative of all patients potentially eligible.

Balancing the advantages and disadvantages of blinding or concealment depends on the specific study question, the nature of treatments being compared, and characteristics of the study settings. We describe below a series of specific questions to inform or guide design decisions regarding concealment or blinding, illustrating with examples from recent real-world clinical.

Questions to Inform Choices Regarding Concealment or Blinding of Treatment Allocation (see Table 1)

Question 1: Will the providers, participants, and raters have expectations regarding likely benefits and adverse effects of study interventions?

Even when investigators perceive equipoise between alternative treatments, study participants or treating clinicians may have strong preferences or expectations regarding differences. In comparisons of new products with treatments in common use, both patients and clinicians may anticipate that a new treatment will be superior. In comparisons of treatments in common use, expectations may be

influenced by media reports or direct-to-consumer marketing. As seen during the COVID-19 pandemic, patient and clinician perceptions regarding highly publicized treatments may be strongly influenced by media reports and high-profile endorsements.⁹ A priori, investigators should consider to what extent evaluations and opinions expressed in popular media, regardless of backing by robust evidence, may influence behaviors or study patients, clinicians, or raters.

Example: The CURVES trial¹⁰ compared efficacy and evaluated dosing of Atorvastatin, Simvastatin, Pravastatin, Lovastatin, and Fluvastatin. Based on an expectation that participants and clinicians would not have strong preferences or expectations regarding differences between these similar treatments, neither participants nor clinicians were blinded to treatment assignment.

Question 2: How might preferences or expectations influence intervention adherence, the fidelity or intensity of the treatment delivered, or the reporting of beneficial or adverse effects?

Participants' or clinicians' expectations, perceptions of treatments, or preferences could affect treatment delivery, adherence to study treatment, as well as the assessment of outcomes. The potential influence of preferences and expectations on treatment delivery or adherence would be expected to increase with treatment duration, treatment complexity, and the need for personalization or adjustment of treatment based on perceived beneficial or adverse effects. Preferences and expectations would be expected to have greater potential to bias assessment of outcomes requiring subjective assessments by participants or clinicians. Those

biases could influence reporting or assessment of both benefits and adverse effects or potential harms.

Example: In the CURVES trial¹⁰ comparing alternative statins using fixed dosing regimens, the efficacy end points were mean percent change in enzymatically-measured plasma LDL cholesterol, total cholesterol, triglycerides, and high-density lipoprotein cholesterol concentrations over 8 weeks of treatment.¹¹ Given the simple dosing profile for each of the study medications and the laboratory-based determination of study outcome, the opportunity for expectations to affect either treatment delivery, patient medication adherence, or outcome assessment was limited. Consequently, neither participants nor clinicians were blinded to treatment assignment.

Question 3: How might those expectations or preferences differ in the settings where trial results will eventually be applied?

If the expectations or preferences of study participants and clinicians are similar to those in real-world settings where study treatments would eventually be delivered, then the effects of those preferences or expectations on treatment delivery or treatment adherence could be considered valid signal rather than noise or bias. In that case, open-label treatment could reveal, rather than obscure, differences between treatments likely to occur in subsequent real-world clinical use.

Example: The PRIDE trial^{11,12} compared the long-acting, monthly-dosed, injectable paliperidone palmitate to oral antipsychotic medication in participants with

schizophrenia. Blinding would have obscured differences in participants' and clinicians' experiences of daily oral medication compared to monthly injections – inherent differences between treatments expected to occur in real-world practice. Consequently, the trial compared open-label treatment, not requiring either placebo pills for participants assigned to injectable medication or placebo injections for participants assigned to oral medication.

Question 4: How might concealing treatment allocation from participants and/or providers reduce biases due to preferences or expectations?

In scenarios where participant, provider, or rater preferences may influence treatment delivery or assessment of outcomes, blinding is certainly preferable if it does not introduce significant burdens or distortions.

Example: The INVESTED trial^{13,14} compared high-dose trivalent and standard-dose quadrivalent influenza vaccine for prevention of death or cardiopulmonary hospitalization in participants with recent myocardial infarction or heart failure. Given the clearly defined treatment protocol and outcomes, a belief in greater effectiveness of a high-dose vaccine might have little influence on delivery of treatment or ascertainment of outcomes. Nevertheless, blinding of alternative vaccine doses would eliminate any potential effect of expectations or preferences while introducing no burden or distortion. Consequently, both participants and clinicians were blinded to group assignment.

Question 5: How might concealing treatment allocation from participants or clinicians obscure meaningful differences between interventions?

When alternative treatments have inherent differences in mode or complexity of delivery (including required frequency of visits or laboratory monitoring), blinding could require significant distortion of one or both treatments. A comparison of those altered treatments could yield results not generalizable to real-world settings where treatments would eventually be delivered.

Example: The InterSePT trial¹⁵ compared risk of suicidal behavior in participants with schizophrenia or schizoaffective disorder treatment with clozapine or olanzapine. Given risk of agranulocytosis, treatment with clozapine required frequent laboratory monitoring. Requiring similar monitoring in both groups would have significantly distorted typical treatment with olanzapine. Consequently, neither participants nor clinicians were blinded, and no artificial conditions were imposed on the olanzapine group.

Question 6: How might procedures necessary to conceal treatment allocation from participants and/or providers impact the acceptability or risk of trial participation?

In addition to reducing generalizability, altering treatments to maintain blinding may reduce overall desirability of trial participation or introduce unnecessary risks.

Example: In the PRIDE trial^{11,12} comparing oral and long-acting injectable antipsychotic medication, blinding participants and clinicians would have required

participants in both groups to both receive monthly injections and use daily oral medication. In such a scenario, the burden on trial participants would be greater than the burden of either treatment in real-world practice. In addition, requiring monthly placebo injections for those assigned to oral medication would create nontrivial risk. These considerations contributed to the choice of an open-label treatment protocol, with each treatment delivered as it would be in everyday practice.

Advantages and Disadvantages of Standardizing Treatment Quality or Intensity

Traditional clinical trials typically compare highly standardized treatments delivered by expert providers in specialized treatment settings. This level of treatment standardization aims to reduce variation in treatment quality, maximizing precision to detect true differences between alternative treatments. In this paradigm, variation in quality or fidelity of treatment would be considered noise rather than signal.

Standardization of treatment, however, may sometimes obscure meaningful differences between treatments that would occur in the real-world settings where trial results would be applied. Naturally occurring variation in treatment might generate signal rather than noise when alternative treatments differ in the resources or expertise required for optimal delivery, the level of adherence necessary for clinical effectiveness, or the burden on participants in terms of

administration and monitoring. The advantages of less “demanding” treatments may only emerge in the less standardized conditions of real-world practice.

Standardization of treatment or follow-up care, however, may sometimes be necessary to protect participant safety. Consequently, some artificial standardization may be necessary in pragmatic trials, even when that standardization might reduce generalizability of findings.

Whether strict standardization of treatment reveals or obscures true differences between treatments under study depends on the specific characteristics of the treatments, study participants, and study settings. We describe below a series of specific questions to inform or guide design decisions controlling or restricting treatment quality, illustrating with examples from recent real-world studies.

Questions to Inform Choices Regarding Standardization of Treatment (see Table 2)

Question 1: How much would the effectiveness or safety of the study treatment(s) vary among providers or care settings and how is this variability related to different levels of resources, experience, or expertise?

If a pragmatic trial aims to evaluate effectiveness and safety under in real-world practice, then it is necessary to consider current variation in practice and to predict how a new treatment might actually be implemented. In many cases, the resources and expertise available in trial settings exceed those available in community

settings where trial results will be applied. The relative effectiveness or safety of alternative treatments may vary according to the expertise with which they are delivered.

Example: The ROCKET AF trial¹⁶ compared rivaroxaban and warfarin for prevention of stroke or thromboembolic event in participants with atrial fibrillation, enrolling participants at 1178 clinical sites in 45 countries. Consistent with good clinical practice, the study protocol called for adjustment of warfarin dosing to maintain international normalized ratio (INR) values within an optimal range. Sites were expected to have a range of expertise in the management of warfarin treatment. As expected, sites varied considerably in the proportion of time that warfarin-treated participants had INR values in that optimal range. Despite this expected real-world variability, between-group differences in effectiveness were similar across sites with higher and lower rates of optimal treatment.

Question 2: What level(s) of resources/experience/expertise are now present in the care settings in which results of this trial will be applied?

When effectiveness or safety would be expected to vary according to the expertise or fidelity with which a treatment is delivered, pragmatic trial investigators should consider the expected practice patterns in settings where trial results would be applied. Matching study treatment with expectations regarding real-world implementation may involve either selection of study sites and/or transparent reporting of variation across study sites.

Example: The RECOVERY platform trial^{17,18} evaluating alternative treatments for COVID-19 aimed to rapidly inform treatment in hospital settings overwhelmed by the pandemic. Strict treatment protocols requiring on-site research staff and significant alterations in care processes were simply not feasible – either in the trial settings or in other similar settings where trial results would be applied. Consequently, study protocols were intentionally flexible, both to facilitate implementation during the trial and maximize generalizability of trial findings to real-world practice.

Question 3: What level(s) of resources/experience/expertise are now present in the care settings in which this trial could be conducted?

Ideally, clinical sites or settings for a pragmatic clinical trial should resemble those in which trial results would eventually be applied. When selecting study sites or evaluating generalizability of results, generators and consumers of real-world evidence may use available data to assess relevant aspects of current practice.

Example: The Salford Lung Study¹⁹ evaluated the efficacy and safety of an innovative combination inhaler (containing fluticasone furoate and vilanterol) to standard inhalers for preventing exacerbations of asthma and chronic obstructive pulmonary disease. Study treatments were delivered in 66 primary clinics of Salford and South Manchester. Including all primary care clinics and pharmacies in a defined geographic area helped assure that study treatment would resemble that in practice settings where trial results would be applied.

Question 4: What special vulnerabilities or risks are anticipated in the study population?

Maximizing generalizability of study results to community practice usually argues for allowing natural variation in study treatments. In some cases, however, standardization of treatment is necessary to protect vulnerable populations or avoid specific risks.

Example: The InterSePT trial¹⁵ comparing clozapine and olanzapine for prevention of suicidal behavior enrolled participants with schizophrenia and either a history of suicide attempt or recent suicidal ideation. Consequently, development of protocols for both clozapine and olanzapine treatment considered appropriate monitoring for suicide risk or other clinical decompensation.

Question 5: Is there some minimal level of treatment standardization necessary for valid inference regarding the study question?

While allowing more variability in quality or fidelity of treatment might improve generalizability to community practice, some minimal level of treatment quality or treatment intensity may be necessary for valid inference regarding the treatments under study. Consequently, treatment protocols in pragmatic trials may require some minimum qualifications for participating clinicians or other mechanisms for assuring a required level of treatment quality.

Example: In the Salford Lung Study,¹⁹ all study treatments were provided by community pharmacies and managed by community primary care physicians. In order to assure adequate delivery of study treatment, all participating pharmacies and physicians received training in good clinical practice and training regarding the novel combination inhaler under study.

Question 6: Is there some minimal or base level of treatment quality necessary to assure participant safety?

Even when standardization of treatment is not necessary for valid inference, some level of standardization or quality control may be necessary to protect vulnerable trial participants. Monitoring and assuring participant safety may require a higher level of standardization than is typical in settings where trial results would be applied.

Example: Given that InterSePT trial¹⁵ participants were at high risk for suicidal behavior, the study protocol called for more frequent visits than would be typical for patients treated with olanzapine. While those more frequent visits could obscure differences between treatments in medication effects on suicidal behavior, more frequent monitoring was considered necessary to protect vulnerable study participants.

Summary and Conclusions

While traditional randomized trials typically examine highly standardized treatments delivered under blinded conditions, both blinding and standardization of treatment may decrease efficiency of evidence generation and/or generalizability of evidence to real-world practice. Pragmatic or real-world clinical trials often involve open label treatment and greater flexibility in treatment delivery. Because those departures from traditional clinical trial practice have the potential to undermine either trial validity or participant safety, designers of pragmatic trials should carefully assess when open-label treatment and/or more flexible treatment protocols are appropriate. We describe a series of specific questions to inform those decisions.

STUDY HIGHLIGHTS

What is the current knowledge on the topic? – Real-world clinical trials are increasing in presence as a response to both the limited generalizability and slow pace of traditional clinical trials.

What question did this study address? – Investigators should systematically determine the application of treatment blinding and standardization of treatment that ensures maximum study validity in trials. However, guidance that incorporates considerations of current practice and demand for meaningful active comparators that inform real-world effectiveness are needed.

What does this study add to our knowledge? – We propose two sets of specific questions to guide the design and application of treatment blinding methods and standardization of treatments in real-world trials with published clinical trial examples to aid investigators in trial design.

How might this change clinical pharmacology or translational science? – Addressing these specific questions should enhance the validity, relevance, speed, and likelihood of completion of real-world trials.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Carolyn Shore of the National Academies of Sciences, Engineering, and Medicine for her support of this project.

Author contributions

Dr. Watanabe wrote the manuscript; Drs. Watanabe, Simon, and Califf designed the proposed framework and synthesis; Drs. Simon, Horberg, Platt, Hernandez, and Califf critically revised the manuscript.

References

1. Corrigan-Curay, J., Sacks, L. & Woodcock, J. Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness. *JAMA* **320**, 867–868 (2018).
2. Eapen, Z. J., Lauer, M. S. & Temple, R. J. The Imperative of Overcoming Barriers to the Conduct of Large, Simple Trials. *JAMA* **311**, 1397–1398 (2014).
3. Sherman, R. E. *et al.* Real-World Evidence - What Is It and What Can It Tell Us? *N. Engl. J. Med.* **375**, 2293–2297 (2016).
4. Forum on Drug Discovery Development and Translation | National Academies. at <<https://www.nationalacademies.org/our-work/forum-on-drug-discovery-development-and-translation>>
5. Medicine, N. A. of S., Engineering, and, Division, H. and M., Policy, B. on H. S. & Translation, F. on D. D., Development, and *Examining the Impact of Real-World Evidence on Medical Product Development: Proceedings of a Workshop Series*. (National Academies Press, 2019).
6. Thorpe, K. E. *et al.* A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J. Clin. Epidemiol.* **62**, 464–475 (2009).
7. Day, S. J. & Altman, D. G. Blinding in clinical trials and other studies. *BMJ* **321**, 504 (2000).
8. Veerus, P., Fischer, K., Hemminki, E., Hovi, S.-L. & Hakama, M. Effect of characteristics of women on attendance in blind and non-blind randomised trials: analysis of recruitment data from the EPHT Trial. *BMJ Open* **6**, (2016).
9. Bull-Otterson, L. *et al.* Hydroxychloroquine and Chloroquine Prescribing Patterns by Provider Specialty Following Initial Reports of Potential Benefit for COVID-19 Treatment — United States, January–June 2020. *Morb. Mortal. Wkly. Rep.* **69**, 1210–1215 (2020).
10. Jones, P., Kafonek, S., Laurora, I. & Hunninghake, D. Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients With Hypercholesterolemia (The CURVES Study)
fn1fn1This study was supported by Parke-Davis, Division of Warner Lambert Company, Morris Plains, New Jersey. Manuscript received August 20, 1997; revised manuscript received and accepted November 24, 1997. *Am. J. Cardiol.* **81**, 582–587 (1998).
11. Alphas, L., Mao, L., Rodriguez, S. C., Hulihan, J. & Starr, H. L. Design and rationale of the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study: a novel comparative trial of once-monthly paliperidone palmitate versus daily oral antipsychotic treatment for delaying time to treatment failure in persons with schizophrenia. *J. Clin. Psychiatry* **75**, 1388–1393 (2014).

12. Alphas, L. *et al.* Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study. *J. Clin. Psychiatry* **76**, 554-561 (2015).
13. Vardeny, O. *et al.* High-dose influenza vaccine to reduce clinical outcomes in high-risk cardiovascular patients: Rationale and design of the INVESTED trial. *Am. Heart J.* **202**, 97-103 (2018).
14. Vardeny, O. *et al.* Effect of High-Dose Trivalent vs Standard-Dose Quadrivalent Influenza Vaccine on Mortality or Cardiopulmonary Hospitalization in Patients With High-risk Cardiovascular Disease: A Randomized Clinical Trial. *JAMA* **325**, 39-49 (2021).
15. Meltzer, H. Y. *et al.* Clozapine Treatment for Suicidality in Schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch. Gen. Psychiatry* **60**, 82-91 (2003).
16. Bansilal, S. *et al.* Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: The Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial). *Am. Heart J.* **170**, 675-682.e8 (2015).
17. Group, T. R. C. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N. Engl. J. Med.* (2020).doi:10.1056/NEJMoa2022926
18. Group, T. R. C. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N. Engl. J. Med.* doi:10.1056/NEJMoa2021436
19. Bakerly, N. D. *et al.* The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in chronic obstructive pulmonary disease. *Respir. Res.* **16**, 101 (2015).