APPENDIX

Adaptive Design Clinical Trials: A Review of the Literature and ClinicalTrials.gov

Systematic Literature Search 1 Phrases and Strategy:
In our first literature review, we used the following phrases, derived from the ten most common types of trial adaptations as described by Shein-Chung Chow and Jen-Pei Liu[1,2]: "phase ii/iii," "treatment switching," "biomarker adaptive," "biomarker adaptive design," "biomarker adjusted," "adaptive hypothesis," "adaptive dose- finding," "pick-the-winner" "drop-the-loser," "sample size re-estimation," "re-estimations," "adaptive randomization," "group sequential," "adaptive seamless," and "adaptive design." We included these terms in different permutations according to the search engines below.

We searched EMBASE on September 16, 2014, using the following terms:
((('phase ii/iii':ab,ti OR 'drop-the-loser':ab,ti OR 'adjustable design':ab,ti OR 'sample size re-estimation':ab,ti OR 're-estimations':ab,ti OR 'adaptive randomization':ab,ti OR 'group sequential':ab,ti OR 'adaptive seamless':ab,ti OR 'multiple adaptive design':ab,ti OR 'treatment switching':ab,ti OR 'biomarker adaptive':ab,ti OR 'biomarker adjusted':ab,ti OR 'adaptive hypothesis':ab,ti OR 'adaptive dose-finding':ab,ti OR 'pick-the-winner':ab,ti) AND ('clinical trial'/de OR 'controlled clinical trial'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'randomized controlled trial'/de)) NOT ('clinical trial (topic' OR 'phase 2 clinical trial (topic' OR 'randomized controlled trial (topic'))
Comment: This search yielded 1,121 results.

We searched PubMed on September 17, 2014, using the following terms:
(("phase ii/iii"[All Fields] OR "treatment switching"[All Fields] OR "biomarker adaptive"[All Fields] OR "biomarker adaptive design"[All Fields] OR "biomarker adjusted"[All Fields] OR "adaptive hypothesis"[All Fields] OR "adaptive dose-finding"[All Fields] OR "pick-the-winner"[All Fields] OR "drop-the-loser"[All Fields] OR "sample size re-estimation"[All Fields] OR "re-estimations"[All Fields] OR "adaptive randomization"[All Fields] OR "group sequential"[All Fields] OR "adaptive seamless"[All Fields] OR "adaptive design"[All Fields]) NOT "Clinical Trials as Topic"[Mesh]) AND Clinical Trial[ptyp]
Comment: This search yielded 329 results.

We searched the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) on September 17, 2014, using the following terms:
"phase ii/iii" OR "adaptive design" OR "treatment switching" OR "biomarker adaptive" OR "biomarker adaptive design" OR "biomarker adjusted" OR "adaptive hypothesis" OR "adaptive dose-finding" OR "pick-the-winner" OR "drop-the-loser" OR "sample size re-estimation" OR "re-estimations" OR "adaptive randomization" OR "group sequential" OR "adaptive seamless"
Comment: This search yielded 428 results.

We searched Web of Science on September 17, 2014, using the following terms:
(TS=("adaptive trial?" OR "flexible trial?" OR "trial modification" OR "modified trial?" OR "phase ii/iii" OR "treatment switching") OR TS=("biomarker adaptive" OR 'biomarker

adjusted" OR "adaptive hypothesis" OR 'adaptive dose-finding" OR "pick-the-winner" OR "drop-the-loser") OR TS=("adjustable design" OR "sample size re-estimation" OR "re-estimation?" OR "adaptive randomization" OR "group sequential" OR "adaptive seamless" OR "adaptive design") AND TS="clinical trial") *AND* DOCUMENT TYPES: (Article OR Abstract of Published Item OR Meeting Abstract)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years
Comment: This search yielded 1,436 results.

Systematic Literature Search 2 Phrases and Strategy:
In our second literature review, we used the following phrases: "interim monitoring," "Bayesian adaptive," "flexible design," "adaptive trial," "play-the-winner," "adaptive method," "adaptive dose adjusting," "response adaptive," "adaptive allocation," "adaptive signature design," "treatment adaptive," "covariate adaptive," "sample size adjustment," and "switch from superiority to noninferiority."
We included these terms in different permutations according to the search engines below.

We searched EMBASE on October 22, 2014, using the following terms:
(('interim monitoring' OR 'adaptive design' OR 'bayesian adaptive' OR 'flexible design' OR 'play-the-winner' OR 'adaptive method' OR (adaptive AND dose AND adjusting) OR 'adaptive trial' OR 'response adaptive' OR 'adaptive allocation' OR 'adaptive signature design' OR 'treatment adaptive' OR 'covariate adaptive' OR 'sample size adjustment' OR (switch AND superiority AND noninferiority)) NOT 'clinical trial (topic)'/exp) AND 'clinical trial'/exp
Comment: This search yielded 388 results.

We searched PubMed on October 22, 2014, using the following terms:
("Interim monitoring"[All Fields] OR "Bayesian adaptive"[All Fields] OR "Flexible design"[All Fields] OR "Adaptive trial"[All Fields] OR "play-the-winner"[All Fields] OR "adaptive method"[All Fields] OR (adaptive[All Fields] AND dose[All Fields] AND adjusting[All Fields]) OR "response adaptive"[All Fields] OR "adaptive allocation"[All Fields] OR "adaptive signature design"[All Fields] OR "treatment adaptive"[All Fields] OR "covariate adaptive"[All Fields] OR "sample size adjustment"[All Fields] OR (switch[All Fields] AND superiority[All Fields] AND noninferiority[All Fields])) NOT "Clinical Trials as Topic"[Mesh] AND Clinical Trial[ptyp]
Comment: This search yielded 86 results.

We searched the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) on October 22, 2014, using the following terms:
'interim monitoring' OR 'bayesian adaptive' OR 'flexible design' OR 'play-the-winner' OR 'adaptive method' OR 'adaptive dose adjusting' OR 'adaptive trial' OR 'response adaptive' OR 'adaptive allocation' OR 'adaptive signature design' OR 'treatment adaptive' OR 'covariate adaptive' OR 'sample size adjustment' OR 'switch superiority noninferiority'
Comment: This search yielded 89 results.

ClinicalTrials.gov Search Phrases and Strategy:
We limited our search of ClinicalTrials.gov to studies that were completed, with results, phases II, II/III, III, and IV. It was necessary to conduct ClinicalTrials.gov searches incrementally because not all search phrases could be entered simultaneously. We searched ClinicalTrials.gov on June 20, 2015 using the following separate sets of terms:
"treatment switching" OR "phase ii/iii" OR "biomarker adaptive" OR "biomarker adaptive design" OR "biomarker adjusted" OR "adaptive hypothesis" OR "adaptive dose-finding" OR "pick-the-winner" OR "drop-the-loser"
Comment: This search yielded 141 results.

"sample size re-estimation" OR "re-estimations" OR "adaptive randomization" OR "group sequential" OR "adaptive seamless" OR "adaptive design"
Comment: This search yielded 99 results.

"interim monitoring" OR "Bayesian adaptive" OR "flexible design" OR "adaptive trial" OR "play-the-winner" OR "adaptive method" OR "adaptive dose adjusting" OR "response adaptive" Comment: This search yielded 30 results.

"adaptive allocation" OR "adaptive signature design" OR "treatment adaptive" OR "covariate adaptive" OR "sample size adjustment" OR "switch from superiority to noninferiority" Comment: This search yielded 34 results.

We imported all results from the literature searches into EndNote X6 and eliminated duplicate entries. We compared the results from ClinicalTrials.gov to the literature search results and eliminated duplicates by hand.

Inclusion and Exclusion Criteria Rationale:

We limited our review to Phase II trials and beyond because trials of these phases are more likely to be submitted to regulatory agencies for consideration as adequate and well- controlled for the purpose of drug approval. As described by the FDA, "the greatest interest in adaptive design clinical trials has been in the adequate and well-controlled study setting intended to support marketing a drug." While Phase III trials are usually expected for purposes of drug approval, Phase II trials are now also accepted as adequate and well-controlled for the purposes of supporting FDA approval.[3] However, we did not include seamless Phase I/II trials, as these trials are virtually always exploratory in nature rather than designed to be adequate and well-controlled. Early-phase experimental research can also more frequently involve adaptations as investigators require flexibility when attempting to understand basic pharmacokinetics, pharmacodynamics, drug dosage levels, and preliminary information on safety and effectiveness.

With regard to defining adaptive dose-finding trials in our review, we included only trials in which researchers used the results of initial dose effects among the first groups of patients enrolled in a trial to determine the doses used or not used among subsequent patients enrolled in the trial. We did not include early exploratory dose-finding trials in which doses were adjusted in a single patient based on that patient's response to the dose level.

Traditionally, group sequential trials have been used to stop trials after interim analyses determining trial futility or efficacy. More recently, group sequential trials have incorporated further adaptive designs that alter studies in different ways following interim analyses.[4] There have been

some conflicting perspectives on whether traditional group sequential trials are adaptive, or whether the adaptive designation only applies to group sequential trials that incorporate options to change study design beyond stopping or continuing the study at interim analysis.[5] The FDA and some biostatisticians describe all group sequential trials as adaptive.[6 7] For example, Chow and Liu include standard group sequential design and adaptive group sequential design in the same category as they define group sequential as "a design that allows for prematurely stopping a trial due to safety, futility/efficacy, or both with options of additional adaptations based on results of interim analysis."[8] However, other biostatisticians describe standard group sequential trials as separate entities from adaptive trials, reserving the "adaptive" designation only for trials that incorporate options to change study design beyond the "standard" group sequential method of stopping or continuing the study at interim analysis.[9 10] Thus, we included only the group sequential trials that are universally accepted as adaptive—those that involve adaptations after interim analyses.

Description of Select Extracted Variables:

When assessing the number of adaptive trials, each trial was counted once, even if the trial used multiple adaptations. Meanwhile, when assessing the prevalence of adaptive methods, as indicated in Figure 2, each use of an adaptive method was counted. Therefore, if a single trial used multiple methods, each method is represented separately in Figure 2. The multiple adaptive category refers to the use of multiple adaptations in a single trial. Methods represented in this category are also listed individually by type. For adaptive group sequential trials, the adaptive group sequential method was noted, as well as the additional adaptation(s) that were made after interim analysis to indicate the frequency of both the adaptive group sequential method as well as the additional adaptation(s) in the study. However, if a group sequential trial included only one adaptation after the interim analysis, this was not considered to be a multiple adaptive trial.

We defined disease type using ICD-9 codes provided by the US Centers for Medicare & Medicaid Services, with the exception that we coded any cancer disease in the general category of oncology, while ICD-9 cancer codes have more subcategories.[11] We categorized diseases as rare if they were included in the National Institutes of Health Office of Rare Diseases Research online Genetic and Rare Diseases (GARD) Information Center.[12] We also categorized diseases as rare if the product under investigation was classified as an orphan drug by the FDA.[13]

We coded clinical and surrogate endpoints according to the definitions provided by the US Institute of Medicine Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease and the National Cancer Institute.[14 15]

We categorized a trial as having found the experimental intervention "effective" if the article explicitly stated a demonstrated therapeutic effect. We categorized a trial as having found a therapy "ineffective" if the trial demonstrated that it did not offer a therapeutic effect or if the trial was terminated due to futility. We categorized a trial as having had inconclusive results if the authors were unable to explicitly determine efficacy or inefficacy. In the case of multiple experimental arms, a trial was categorized as having found an experimental intervention effective if the authors explicitly stated that at least one experimental intervention arm demonstrated a therapeutic effect.

When categorizing trial location, trials occurring in one or more Western European nations were coded as occurring in Western Europe, while trials occurring in more than one nation including at least one nation outside of Western Europe were categorized as multinational.

Trial duration was calculated from first patient entering to last patient exiting trial.

We also assessed whether articles included information on participants with other demographic characteristics (disability, prisoner, resident of other state or private institution, student, military

personnel or veteran, or any other unanticipated demographic markers or patient characteristics). Finding none, we did not report on these variables.

With regard to categorizing trial adaptations as well-understood or less well-understood, the FDA guidance has specifically described what would cause a trial to fit either category. Some types of adaptations fall rather squarely within a category, while for several types of adaptations, the FDA delineates different permutations of the adaptations that would qualify a trial as either well-understood or less well-understood.[16] Thus, to determine a trial's category, it was usually necessary to determine the specific form of the adaptation. The following FDA categorizations applied to the trials in our survey:

- Adaptive hypothesis trials were less well-understood because they involved switching between primary and secondary endpoints based on interim estimates of treatment effects.
- The adaptive treatment-switching trial was less well-understood because it involved a highly flexible modification based on un-blinded interim assessment of treatment effects.
- Adaptive dose-finding trials were well-understood when dropping a dose due to toxicity unrelated to efficacy and were less well-understood when doses were adjusted based on measures of efficacy.
- Pick-the-winner/drop-the-loser trials were well-understood when dropping arms for safety concerns unrelated to efficacy and were less well-understood when measuring efficacy based on un-blinded interim analyses.
- Sample size re-estimation trials were well-understood when based on blinded interim analysis to maintain study power or when used with group sequential designs reducing sample size for pre-planned early termination following demonstration of efficacy/inefficacy, as determined by an independent data monitoring committee and were less well-understood when un-blinded and based on interim-effect estimates.
- Adaptive randomization trials were less well-understood.
- Adaptive group sequential trials were well-understood when used for early stopping for efficacy/inefficacy and/or in combination with another well-understood adaptive design and were less well-understood when used in combination with another less well- understood adaptation(s).
- Trials using multiple adaptations were less well-understood.
- The single trial using an "other" type of adaptation was also a seamless Phase II/III trial, and so it involved multiple adaptations and was less well-understood.

As statistical work expands on adaptive designs, well and less well-understood adaptive method categorizations may change. The FDA guidance did not specify whether seamless Phase II/III trials were well-understood or less well-understood because the guidance expressly did not discuss seamless Phase II/III trials. Their rationale for excluding Phase II/III trials was that after interim analysis in a Phase II/III trial, the study changes from having features of an exploratory trial to having features of an adequate and well-controlled trial, without adding any other meaning to the design beyond that captured by the inclusive term, "adaptive."[17] Therefore, we have not classified seamless Phase II/III trials as either well-understood or less well-understood. However, we have included Phase II/III trials in other parts of our study because seamless designs are usually included among the major types of adaptive designs in the medical literature.

For our evaluations of how trials were used in regulatory product approval considerations, product review documents were only available for approved products from the FDA, while EMA review documents were available for both approved and rejected products. Also, we looked at EMA drug reviews but did not examine drug reviews from agencies of individual European nations. For the

three studies that were conducted in Japan, we sought data on whether adaptive trials were used for approval consideration by Japan's Pharmaceuticals and Medical Device Agency; however, we were unable to locate this data.

To determine whether adaptive trials were the final trials in product review documents, we compared the date of completion of the adaptive trial to the completion dates of other trials in the approval documents. Adaptive trials were recorded as pivotal when agencies explicitly referred to them as such.

We recorded the number of days between New Drug Applications and FDA drug approval to assess length of time required by the FDA to review applications including adaptive clinical trials. Similarly, to assess the length of time for EMA review of product packages with adaptive trials, we recorded the time between submission of a marketing application to the EMA and the agency's decision on marketing authorization or rejection.

FDA and EMA orphan designations provide incentives for research on treatments of rare diseases affecting small portions of the population. The FDA gives orphan status to drugs and biologics intended for the safe and effective treatment, diagnosis or prevention of rare disease/disorders that affect fewer than 200,000 people in the US or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.[18] The EMA defines orphan medicines according to the following criteria: 1) intended for the treatment, prevention, or diagnosis of a disease that is life-threatening or chronically debilitating; 2) prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and 3) no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.[19]

Exclusion Rationale for Specific Clinicaltrials.Gov Variables:

ClinicalTrials.gov listings are different from the format of published articles. Some of the variables from our main search were not available on ClinicalTrials.gov, and reporting norms for ClinicalTrials.gov differed from those of published articles. Hence, we have included in our main analysis only the ClinicalTrials.gov variables that could be assessed with the results from published articles. Accordingly, we included in our main analysis the following variables from ClinicalTrials.gov: adaptive design type; research phase (II, seamless II/III, III, IV); disease type; whether the disease was rare; whether mortality was an endpoint; types of trial endpoints; intervention type (prescription drug, medical device, or other type of intervention); trial location; funding sources (industry, government, other); trial duration; subject population sample size; patient demographic data (age, race, gender); and use of the trials in FDA and EMA evaluations of new products.

We included ClinicalTrial.gov data in our results on trends in adaptive trial types over time. ClinicalTrials.gov launched in 2000, adding to our review more adaptive trials in recent years. However, even without the ClinicalTrials.gov results, we still found in the published literature a dramatic expansion of adaptive trials since the mid-1990s, with particular expansion since 2010.

We did not determine from ClinicalTrials.gov whether interventions were found effective or ineffective, as trial sponsors usually reported detailed results on ClinicalTrials.gov but did not explicitly provide summarizing conclusions based on those results. We did not assert our own conclusions based on the results. We did not include author location, as this was not consistently available. ClinicalTrials.gov listed investigator information, but this often referred to trial sponsors, who did not always list specific authors or their locations. Further, given the inconsistency with which authors were listed, we also did not record author affiliation. While we deemed the ClinicalTrials.gov

reporting on basic types of adaptive designs to be available approximately commensurate to such availability in article results, we did not classify ClinicalTrials.gov listings as "well-understood" or "less well-understood," because many ClinicalTrials.gov listings did not provide methods descriptions with sufficient details to definitively ascertain whether the version of adaptation deployed would qualify as well-understood or less well-understood.

We did not include ClinicalTrials.gov results on independent data monitoring committees or blinded interim analyses in our main results because the ClinicalTrials.gov methodology descriptions were significantly less detailed than methodology descriptions in published trials. It is therefore likely that an absence of reporting of independent data monitoring committees or blinded interim analyses for ClinicalTrials.gov listings reflects the overall limited reporting of trial methodology details on the website, rather than actual use of these safeguards.

ClinicalTrials.gov provides trial information without necessarily having a level of detail necessary for the research community to interpret and rely on the study results, which is a primary objective of published articles, and why published articles should be expected to report on these important safeguards for adaptive trial integrity. Therefore, we deemed it appropriate to assess reporting of independent data monitoring committees and blinded interim analyses for published trials in our main results, but not for ClinicalTrials.gov listings. While a number of studies on ClinicalTrials.gov indicated that they had data monitoring committees, only one explicitly stated that the committee was independent. Two studies on ClinicalTrials.gov mentioned a blinded interim analysis.

Supplementary Sampling Method:

For the supplementary sampling of published conventional randomized controlled trials (RCTs), one author (LB) systematically sampled RCTs as they appeared in academic literature in five-year increments between 1976 and 2014. The sample was conducted in English using the search phrase "randomized controlled trial" in the Columbia University Library E-Resources Find Articles site, using the Advanced Search option to restrict results to five-year increments.[20] The E-Resources Find Articles site relies on the Summon Key Databases and Packages, a comprehensive collection of online journals.[21] The sample was taken October-December 2012 for the years 1976-1990, and January-February 2015 for the years 1991-2014. For each five-year period, approximately 50 articles were collected by sorting results chronologically and using the following sampling equation: (Total number of results in the five-year period sampled)/50 = N. Approximately every Nth article was sampled. If the sampled article was an RCT, data were recorded on types of interventions and participant race. 383 articles were included. Given that sample size and duration of adaptive trials were analyzed by phase, sample size and duration of RCTs from the supplementary sample were also analyzed by phase. From the standard RCT results, 50 Phase II and 50 Phase III trials were selected for the same years in which adaptive trials of the same phases appeared. Fewer adaptive trials were found in the late 70s and 80s while they increasingly occurred from 1998 onward. Thus, fewer Phase II and III conventional RCTs were selected from the late 70s and 80s and incrementally more were selected from 1998 onward. These trials were screened for adaptive designs and none were found. Trends in sample size and duration of these standard RCTs were recorded. We calculated the median and inter-quartile range of trial duration and sample size, separately for Phase II and Phase III adaptive and standard trials. Analyses of sample size and duration of standard and adaptive trials were conducted in Stata, version 13 (College Station, TX).

Comparisons of Trends in Sample Size and Duration of Adaptive vs. Non-Adaptive Clinical Trials:

Three adaptive trials were also selected from the results of our review and for each of these three trials, one author (LB) searched the medical literature for three additional comparable standard RCTs of the same phase testing similar therapeutics for the same conditions. Another author (AK) checked the selections of comparable trials. Duration and sample size were compared among these subsets of like trials. The three adaptive trials were selected from the results of our systematic review in disease areas that featured prominently in our results—oncology and circulatory system disorders.

Adaptive trials were chosen that investigated treatments for which there was a considerable quantity of extant published research. This made it possible to locate roughly comparable standard trials of the same phase testing similar therapeutics for the same conditions. Sample size and duration of the adaptive trials are compared with those of the similar non-adaptive trials in the table below. While total trial duration was not listed in the Brass et al. study, trial duration was ascertained through correspondence with the lead study author.

These sub-analyses of like studies did not indicate consistent differences in sample sizes and durations of adaptive and standard trials. Ultimately, it is difficult to compare duration or sample sizes of adaptive and traditional trials when the studies are not designed in exactly the same way, varying only by using an adaptive or traditional design. Opportunities for such comparisons are rare, while they have been modeled.[22]

Appendix Table 1. Comparisons of Sample Size and Duration in Similar Adaptive and Non-Adaptive Clinical Trials

Examples of Individual Clinical Trials	Sample Size	Duration (weeks)
Adaptive Trial from Systematic Review		
Lewis et al.[23]	**199**	**88**
Other Similar Non-Adaptive Published Trials		
Brass et al.[24]	391	130
Lievre et al.[25]	164	69
Nwose[26]	190	100
Adaptive Trial from Systematic Review		
Fink et al.[27]	**680**	**184**
Other Similar Non-Adaptive Published Trials		
von Pawel et al.[28]	637	134
Schmittel et al.[29]	226	300
Baka et al.[30]	370	372
Adaptive Trial from Systematic Review		
Goldstein et al.[31]	**2753**	**115**
Other Similar Non-Adaptive Published Trials		
Steg et al.[32]	1258	70
Mega et al.[33]	3491	96
Alexander et al.[34]	402	91

Appendix Table 2. Examples of Published Adaptive Trials Used in FDA and EMA Approval Consideration

Published trial	Year	Drug Tested	Disease	Trial used for EMA Approval Consideration	Trial used for FDA Approval Consideration	Adaptive Features	Dropped Arm for Futility	FDA Priority Review	EMA Accelerated Assessment	Reference Citation Number
Lewis *et al.*	1997	Cidofovir	Cytomegalovirus Retinitis	Yes	Yes	Seamless Phase II/III	No	No	No	35
Mauck *et al.*	1999	FemCap	Contraception	No	Yes	Seamless Phase II/III	No	No	No	36
Pfaffenrath *et al.*	2002	Tanacetum parthenium	Migraine Headache	Yes	No	Sample size re-estimation, Adaptive group sequential	No	No	No	37
Matthys *et al.*	2003	Pelargonium Sidoides (EPs 7630)	Acute Bronchitis	Yes	No	Adaptive group sequential	No	No	No	38
Tanko *et al.*	2003	Ibandronate	Postmenopausal Bone Loss	No	Yes	Seamless Phase II/III	No	No	No	39
Muenzer *et al.*	2006	Idursulfase	Hunter syndrome	Yes	Yes	Seamless Phase II/III	No	Yes	No	40
Lizogub *et al.*	2007	Pelargonium Sidoides (EPs 7630)	Common Cold	Yes	No	Sample size re-estimation, Adaptive Group Sequential	No	No	No	41
Gross *et al.*	2007	Polyphenon® E	External Genital Warts	No	Yes	Seamless Phase II/III	No	No	No	42
Bachert *et al.*	2009	Pelargonium Sidoides (EPs 7630)	Acute Rhinosinusitis	Yes	No	Sample size re-estimation, Adaptive group sequential	No	No	No	43
Barnes *et al.*	2010	Indacaterol	COPD	Yes	Yes	Seamless Phase II/III	No	No	No	44
Matthys *et al.*	2010	Pelargonium Sidoides (EPs 7630)	Acute Bronchitis	Yes	No	Sample size re-estimation, Adaptive Group Sequential	No	No	No	45
Skrivanek *et al.*	2014	Dulaglutide-Metformin	Type 2 Diabetes	Yes	Yes	Adaptive dose finding, Pick-the-winner/Drop-the-loser, Adaptive group sequential, Seamless Phase II/III, Multiple adaptive	No; (dropped for safety)	No	No	46

Confirmatory Analyses:

Sampling of Trials

One limitation of this review is that adaptive trials may not explicitly state the adaptive method name in publications or on ClinicalTrials.gov listings. Thus, we supplemented our results by evaluating in-depth a systematic sample of all published clinical trials listed in PubMed at 10-year intervals (1973, 1983, 1993, 2003, and 2013) to assess the fraction that used adaptive designs. Similar to the systematic review, we included only Phase II trials or beyond and relied on the FDA guidance definition for adaptive designs as trials that involve pre-planned alterations to trial design after interim analysis of accumulating trial data.[1] We retrieved every current clinical trial indexed in PubMed using the search phrase: clinical trial[pt]. We limited the search to the above years. For each year, we took a random sampling of 50 published trials using the equation: (total number of articles that appeared for the search term in the particular year sampled)/50 = N. Every Nth article was obtained (or the next closest article in the results list when the Nth article was irretrievable or a Phase I trial), and read in full to check for adaptive designs. One researcher (DP) completed initial data extraction and another (LB) checked the assessment of adaptive methods. This sampling of 250 published trials revealed only two adaptive trials—one in 1973 and one in 2003.

Journal Reporting

To further assess the proliferation of adaptive design methods, editors of ten leading medicine Journals by Rank in Journal Citation Reports were contacted by one researcher (DP) to inquire approximately how many adaptive design trials they receive as submissions each year.[47] Editorial staff at eight of ten leading journals responded to our inquiry regarding the frequency with which they receive adaptive design trial submissions. Of the eight, four said that they rarely or never receive such trials and four said they had no way of estimating a response.

Similar Published Analysis

Another survey of 291 clinical trials published in *JAMA*, *NEJM*, *BMJ*, and *The Lancet* in 2006, also found adaptive designs uncommon. Out of all surveyed trials, 2 of 194 multicenter trials were adaptive, while the design was unclear in 18 of the multicenter trials. Similarly, 1 of 97 single center trials had an adaptive design, and the design was unclear in 17 single center trials.[48] It is possible that the author's findings may have included a smaller number of adaptive trials in part due to a lack of explicit reporting of adaptive design use, particularly given the number of trials in which design was unclear. This seems to be a persistent for efforts to assess the frequency of the use of adaptive designs.

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