Best Practices for the Design, Implementation, Analysis, and Reporting of Oncology Trials with High Rates of Treatment Switching

A Guidance Document from the Green Park Collaborative

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# TABLE OF CONTENTS

INTRODUCTION .................................................................................................................................................. iii
PRIOR WORK ......................................................................................................................................................... iii
CMTTP WRITING AND EDITORIAL TEAM ............................................................................................................... iv
FUNDING .............................................................................................................................................................. iv
ACKNOWLEDGEMENTS ........................................................................................................................................ iv
SUMMARY OF RECOMMENDATIONS ................................................................................................................... vii
RECOMMENDATIONS .......................................................................................................................................... 1

## SECTION I: WHETHER AND WHEN TO ALLOW TREATMENT SWITCHING ................................................. 1

- Recommendation 1: When Treatment Switching Should Not Be Allowed ...................................................... 1
- Recommendation 2: When Treatment Switching Should Be Allowed .............................................................. 1
- Recommendation 3: When It Is Uncertain Whether to Allow Treatment Switching ........................................ 2
- Recommendation 4: Treatment Switching Trigger Event .................................................................................. 2

## SECTION II: KEY ANALYTICAL METHODS AND DECISION DOCUMENTATION .................................. 5

### Section A: Selecting Analytical Adjustment Methods at the Study Design Phase

- Recommendation 5: Excluding and Censoring Switchers ............................................................................... 5
- Recommendation 6: Initial Evaluation of Analytical Adjustment Methods ..................................................... 6
- Recommendation 7: Designing the Trial to Maximize the Use of Potential Adjustment Methods .................. 7

### Section B: Use of Evidence from Sources Other Than the Clinical Trial

- Recommendation 8: Searching for External Evidence .................................................................................... 9
- Recommendation 9: Fitness of External Evidence .......................................................................................... 9
- Recommendation 10: Uses of External Evidence .......................................................................................... 10

### Section C: Decision Documentation

- Recommendation 11: Contents of Protocol and Statistical Analysis Plan ......................................................... 13

### Section D: Final Analytical Method Selection and Reporting

- Recommendation 12: Final Selection of Analytical Methods .......................................................................... 13
- Recommendation 13: Reporting Selection of Analytical Methods and Results ...................................... 17
- Recommendation 14: Reporting Analyses of External Evidence to Decision Makers ................................. 18

## SECTION III: STAKEHOLDER INVOLVEMENT IN THE STUDY DESIGN PROCESS ............................... 20

- Recommendation 15: Directly Affected Stakeholders: Patients and Clinicians ........................................... 20
- Recommendation 16: Ethical Review Boards ................................................................................................. 21
- Recommendation 17: Regulators, Health Technology Assessors, and Payers ............................................. 22

## SECTION IV: INFORMED CONSENT: PROCESS AND CONTENT ................................................................. 24

- Recommendation 19: Informed Consent Process: Drafting the Consent Form ........................................... 25
Recommendation 20: Informed Consent Content...

SECTION V: SUPPLEMENTAL RECOMMENDATIONS

Recommendation 21: Pre-Competitive Cooperative Research

Recommendation 22: Clinical Trial Results Reporting and Data Sharing

APPENDIX 1: REVIEW OF SELECTED STATISTICAL ANALYTICAL METHODS

APPENDIX 2: EVALUATING THE QUALITY OF EXTERNAL EVIDENCE AND DATA SOURCES

APPENDIX 3: SAMPLE INFORMED CONSENT LANGUAGE

APPENDIX 4: INFORMED CONSENT AT STUDY ENTRY: TREATMENT SWITCHING CHECKLIST

APPENDIX 5: INFORMED CONSENT AT TIME OF PROGRESSION: TREATMENT SWITCHING CHECKLIST

CITATIONS
INTRODUCTION
Treatment switching from the control to experimental arms in a clinical trial is a common occurrence in studies of oncology drugs and has raised questions about how these trials can best be designed, managed, analyzed, and interpreted. While there are ethical and other factors that can lead to high rates of treatment switching, this situation creates a number of significant challenges for the accurate interpretation of trial findings. Trials with significant rates of switching can be difficult to evaluate for regulatory purposes, and are particularly problematic in the assessments done in the context of reimbursement and pricing decisions.

Payers and health technology assessment (“HTA”) organizations differ significantly in their familiarity with and views on acceptable approaches to manage treatment switching, as well as the methods used to adjust trial results to account for switching. This variability in approach creates significant uncertainty for drug developers when designing clinical development programs for oncology drugs, and when presenting their results in the context of market access decisions. In addition, the methods used in this context are complex and evolving.

This document provides recommendations on how best to design and implement oncology drug studies in which high rates of treatment switching are expected, when one purpose of these studies is to produce evidence for consideration by payers, health technology assessment organizations and clinical guidelines developers.

This guidance document aims to provide greater clarity and consistency about the expectations of payers, HTA organizations, guideline developers, and other key decision makers when assessing evidence from oncology trials in which substantial treatment switching has occurred. The intent is for the advice in this document to be considered by life sciences companies in designing and presenting their oncology clinical development programs, and by organizations that analyze this evidence to inform market access decisions.

The recommendations in this document were developed through extensive dialogue and consultation with a broad range of experts and stakeholders, including payers, patients, clinicians, methodologists, and drug companies. Discussions took place through an in-person meeting, numerous conference calls, and extensive electronic communication. While the recommendations do not reflect a formal consensus of the project participants, we have invested considerable effort in reflecting the views of all stakeholders in the advice offered. As with all other guidance, the recommendations are not intended to be binding on life sciences companies, payers, HTA groups, or others.

PRIOR WORK
The project that generated this guidance document builds on work that was conducted in 2014, with support from Bellberry Ltd (a national, private, not-for-profit organization in Australia) and led by Chris Henshall. That effort included a meeting of a group of international experts and stakeholders in Adelaide, South Australia, to identify the issues and areas of agreement on appropriate approaches to addressing treatment switching in the design and analysis of oncology trials, and to determine where further work was needed. Detailed reviews of the issues discussed at that workshop have recently been published in a pair of papers in the International Journal of Technology Assessment in Health Care.1,2 In brief, the 2014 workshop identified a number of themes that emerged regarding the ethical, scientific, and practical issues associated with treatment switching.
Best Practices for the Design, Implementation, Analysis, and Reporting of Oncology Trials with High Rates of Treatment Switching

First, treatment switching has become an established part of many oncology trials. In situations where valid alternative treatments are lacking, patients are less likely to join or remain in trials that do not allow treatment switching when patients think they should. Patients and patient advocates need to be involved in the design of trials and in managing treatment switching so as to ensure that the interests of those participating in a trial are respected while maximizing new knowledge that will help those who will be treated in the future.

Second, patient demand for treatment switching and the challenges that such switching presents for the interpretation of trial results depend upon the nature and stage of the disease, the nature of the primary and secondary endpoints being studied, and the nature of the treatments currently available for patients in the trial and at later stages in their disease. There is no single optimal approach to treatment switching; whether or not it should be allowed, and in what circumstances, depends on the context.

Third, there is no single optimal approach to analyzing and interpreting the data from trials in which treatment switching has occurred. The choice of methods will depend upon the nature of the trial, the extent of treatment switching and the point(s) at which it has occurred, the extent to which the assumptions of different statistical approaches are met and can be shown to be met within the setting of the trial, and the availability of data to support the application of those approaches.

One of the suggestions emerging from that activity was the need for more detailed guidance on good practices in the design, implementation, analysis, and reporting of oncology trials with high rates of treatment switching. That observation was the basis for the current project and the proposed guidance provided in this document.

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CMTP would also like to acknowledge all those who attended the in-person meeting in October 2015, offered their views on these issues, and reviewed drafts of these best practices. Their affiliations included: ASCO; Brunel University London; Department of Health, Australian Government; ECRI

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Many thanks to the following CMTP staff members for their dedication and hard work to make this project successful: Donna A. Messner, Senior Vice President; Jennifer Al Naber, Program Manager, Green Park Collaborative; Julie Simmons, Manager, Marketing and Communications; Marty Johnson, Marketing and Project Coordinator; and Janelle King, Executive Assistant. We would also like to thank Scott Allocco, President of SJA Healthcare Strategies, for his steadfast support on this project.
### SUMMARY OF RECOMMENDATIONS

**SECTION I: WHETHER AND WHEN TO ALLOW TREATMENT SWITCHING**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td><strong>When Treatment Switching Should Not Be Allowed</strong>&lt;br&gt;Treatment switching should not be allowed in clinical trials in which the experimental agent has little or no intrinsic activity but is used to modulate the efficacy of other active agents.</td>
</tr>
<tr>
<td>2</td>
<td><strong>When Treatment Switching Should Be Allowed</strong>&lt;br&gt;Researchers and sponsors should allow and plan for treatment switching in the following circumstances: (1) when the experimental therapy is already available on the market where the study is taking place; (2) when a surrogate endpoint is validated and predictive of overall survival and will be ascertained during the trial; (3) when an intermediate endpoint is highly relevant to patients.</td>
</tr>
<tr>
<td>3</td>
<td><strong>When It Is Uncertain Whether to Allow Treatment Switching</strong>&lt;br&gt;In situations where it is not clear whether or not treatment switching should be allowed, researchers and sponsors should consult with patients, patient advocates, and clinicians, and also consider the views of regulators, health technology assessors, and payers in assessing its appropriateness.</td>
</tr>
<tr>
<td>4</td>
<td><strong>Treatment Switching Trigger Event</strong>&lt;br&gt;If treatment switching is allowed, researchers and sponsors should carefully consider and clearly define in the study protocol the trigger event that marks when patients in the control group will be allowed to switch to the experimental therapy as well as who will determine whether or not the trigger event has occurred. Treatment switching should not be allowed before that time and the relationship between the frequency of monitoring and the trigger event should be explicitly considered. In order to preserve the possibility of using certain adjustment methods, researchers may need to define a window of time during which a patient can switch treatments, beginning with the trigger event and ending soon thereafter.</td>
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**SECTION II: KEY ANALYTICAL METHODS AND DECISION DOCUMENTATION**

#### A: Selecting Analytical Adjustment Methods at the Study Design Phase

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<tr>
<td>5</td>
<td><strong>Excluding and Censoring Switchers</strong>&lt;br&gt;It is generally not appropriate to adjust for treatment switching either by excluding switchers from the analysis or by censoring them at the time of the switch.</td>
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<tr>
<td>6</td>
<td><strong>Initial Evaluation of Analytical Adjustment Methods</strong>&lt;br&gt;Clinical study sponsors and researchers should consider the following factors in evaluating analytical methods that can be used to adjust study results for treatment switching: (1) the likelihood of the method’s underlying assumptions being true, including assessment of the completeness of the list of covariates that affect relevant outcomes and also predict treatment switching; (2) the size of the anticipated treatment effect and whether it is likely to persist after the drug is discontinued; (3) the anticipated level of treatment switching; (4) the size of the study; (5) whether the control group will have an active therapy; (6) the timing of any allowed treatment switching; and (7) whether quality external data, including observational data, are available to support assumptions or to calculate counterfactual survival times (see Section II.B and Appendix 2). Although it may not be possible to decide definitively before the trial data become available what the primary analytical method should be, sponsors and researchers should have a good sense of the probabilities and be able to articulate the standards and criteria they will use to make that decision.</td>
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### Recommendation 7: Designing the Trial to Maximize the Use of Potential Adjustment Methods

To the extent possible, sponsors and researchers should design the clinical trial to maximize the potential of using all recommended statistical adjustment methods that may have to be used. The most important action to take in this regard is to ensure that all data relevant to adjusting for treatment switching are collected at the appropriate times.

### B: Use of Evidence from Sources Other Than the Clinical Trial

#### Recommendation 8: Searching for External Evidence

Researchers and sponsors should systematically search for data from sources other than the clinical trial, including both randomized clinical trials and observational data, to help support analytical approaches used to adjust for treatment switching.

#### Recommendation 9: Fitness of External Evidence

Clinical study sponsors and researchers should assess external data and data sources they are considering using to support their chosen analytical adjustment method in order to be sure that the data are fit for their intended use.

#### Recommendation 10: Uses of External Evidence

When feasible, researchers should integrate appropriate external data with data from a clinical trial that includes treatment switching for the following purposes: (1) predicting counterfactual survival times in patients who switch; (2) examining treatment switching adjustment methodology assumptions; and (3) evaluating the relationship between overall survival and earlier surrogate endpoints (e.g., objective response rate or progression-free survival).

### C: Decision Documentation

#### Recommendation 11: Contents of Protocol and Statistical Analysis Plan

Investigators should document in the protocol the key decisions and procedures relating to treatment switching, as well as their underlying rationales. Fundamental topics that should be addressed (if applicable) include: whether or not treatment switching will be allowed during the trial and why; the conditions or times when treatment switching will be allowed and why; any trigger event chosen and why (including the study’s definition of “progression” if that is a trigger event); whether there will be any additional costs to patients if they switch and why; what external evidence investigators will examine, what analyses will be performed on it, and how the results will be used; and what data relevant to treatment switching will be collected at which times, how long data collection will continue, and why.

Investigators should also identify either in the protocol or in the statistical analysis plan (“SAP”) the most likely appropriate statistical analysis methods (evaluated as described in Section II.A) and state how each method will be analyzed at the conclusion of the trial, following a six-step process to determine its suitability (see Recommendation 12). The investigator should set forth the criteria for selecting the primary methodology, identifying which other methodologies should be applied for purposes of comparing results for consistency, and what other sensitivity analyses will be performed. Any external data sources to be examined and their uses should also be documented a priori.

The SAP should provide more technical and detailed explanations of the procedures that will be followed to execute the analyses above. While the demarcation between the information that should be in the protocol and the information that should be in the SAP is not always distinct, in general, the protocol should set forth what analyses will be performed and why, while the SAP sets forth details about how the analyses will be performed.
D: Final Analytical Method Selection and Reporting

Recommendation 12: Final Selection of Analytical Methods
When clinical trial data become available at the conclusion of the study, investigators should follow a six-step process to assess which analytical methods are appropriate: (1) conduct an initial screen; (2) assess the number and proportion of switchers and non-switchers in the control group; (3) assess the key assumptions; (4) examine the output and performance of the methods; (5) perform extrapolation if needed; (6) review sensitivity analyses and any information from external data.

Recommendation 13: Reporting Selection of Analytical Methods and Results
The results of the final selected primary analytical method should be provided to reviewing regulators, HTA entities, and payers, along with all justifications for the method’s selection, supporting and opposing evidence, uncertainties identified, and an assessment of how well it worked. Fundamental data that should be provided regardless of adjustment method used (if any) include baseline characteristics for switchers and non-switchers, information on who switched over time, and measures of switching both as percentage of patients who switched and the amount of exposure and follow-up time they contributed. The results of the intention-to-treat analysis should always be provided to reviewers. All other methods considered by the investigators should be reported and discussed as well. If any analyses were performed using those methods, the results should be provided; if any of the key alternative adjustment methods were ruled out, the rationales must be supplied. The degree of detail provided about the analyses must be sufficient to allow reviewers to clearly understand what specific analyses were undertaken and the methodology employed. Similar standards for the reporting of analytical methods and results in the medical literature also need to be developed to provide transparency and consistency.

Recommendation 14: Reporting Analyses of External Evidence to Decision Makers
Along with any analyses of external evidence that they provide to decision makers, clinical study sponsors and researchers should include: (1) their assessments of the external data quality and fitness; (2) brief information on external data sources they considered but did not select along with an explanation of the decision; (3) results of all analyses conducted; (4) results of sensitivity analyses and, when appropriate, model validation; and (5) their a priori specification of the data source to be used or the criteria to be used for its selection and the analyses to be performed. Any analyses performed that were not specified a priori should be clearly identified.

SECTION III: STAKEHOLDER INVOLVEMENT IN THE STUDY DESIGN PROCESS

Recommendation 15: Directly Affected Stakeholders: Patients and Clinicians
Study sponsors and researchers should involve stakeholders who may be directly affected by treatment switching, such as patients and clinicians, in the clinical trial design and development processes relating to treatment switching. Stakeholder involvement should begin with the trial conceptual stage and continue throughout the trial with respect to any potential change in protocol or study design that involves treatment switching.

Recommendation 16: Ethical Review Boards
Entities such as Institutional Review Boards or Research Ethics Committees that conduct ethical reviews of proposed trials should require study sponsors and researchers to include patients and clinicians in the study design processes relevant to treatment switching, beginning with the trial conceptual stage. They also need to assure themselves that the trial design and analysis plans relating to treatment switching will allow valid and robust answers to be derived for the trial questions posed.
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<th>Recommendation 17: Regulators, Health Technology Assessors, and Payers</th>
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<tr>
<td>Stakeholders such as regulators, health technology assessors, and payers, who are not directly affected by treatment switching but who have substantial interest in the study results and whose interpretations of those results will directly affect market or patient access, should be receptive to requests from study sponsors and researchers to discuss issues about treatment switching. Appropriate topics include (a) the stakeholder’s position on the recommendations in this document on the design and analysis of trials in which treatment switching is expected, (b) aspects of treatment switching that this document does not address, and (c) uncommonly challenging situations concerning treatment switching.</td>
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<tr>
<th>SECTION IV: INFORMED CONSENT: PROCESS AND CONTENT</th>
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<td><strong>Recommendation 18: Informed Consent Process: Two Critical Stages</strong></td>
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<td>Clinicians responsible for obtaining informed consent should be particularly sure to provide key information about treatment switching at two critical times: (1) when patients are considering whether to enter the trial, and (2) when they are considering switching treatments.</td>
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| **Recommendation 19: Informed Consent Process: Drafting the Consent Form** |
| Researchers should involve patients and/or patient advocates in drafting the consent form language regarding treatment switching. |

| **Recommendation 20: Informed Consent Content** |
| When patients are considering whether or not to participate in an oncology drug clinical trial, informed consent should include (1) an explanation of clinical research and the rationale for conducting the trial, (2) a complete description of treatment switching (including whether or not it will be available during the study, the conditions under which it may be available, and the rationales for those decisions), and (3) the need for long-term data and follow-up in order to preserve the possibility of adequately adjusting for switching. |

When patients participating in an oncology drug clinical trial are deciding whether or not to switch treatments, their treating physician should present them with (1) all treatment options, (2) more specific details about the treatment switching process, and (3) a review of the importance of long-term data and follow-up in order to preserve the possibility of adequately adjusting for switching. |

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<th>SECTION V: FUTURE STEPS</th>
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<td><strong>Recommendation 21: Pre-Competitive Cooperative Research</strong></td>
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<tr>
<td>Study sponsors and researchers who share a common interest in a broadly applicable or fundamental scientific issue relating to treatment switching, such as the identification and validation of surrogate outcomes for overall survival, should ideally undertake appropriate research as a joint endeavor.</td>
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| **Recommendation 22: Clinical Trial Results Reporting and Data Sharing** |
| In order to help maximize the utility of these best practices, stakeholders should support initiatives to (1) ensure that all clinical trials are publicly registered and results reported, and (2) encourage the sharing of data on the individual patient level provided that appropriate safeguards are in place to protect the interests of patients, researchers, and sponsors. Research funders should make funding contingent on recipients registering the study and providing the results. Before deciding to participate, patients and clinicians should consider whether sponsors and researchers plan to register the study and share its results, which actions would help maximize the value of their participation and contributions. |
### APPENDICES: EVALUATING THE QUALITY OF EXTERNAL EVIDENCE AND DATA SOURCES

**Recommendation Appx-1: Quality of External Evidence and Data Sources**

Clinical study sponsors and researchers should systematically assess the quality of any external data and data sources they are considering using to support their chosen analytical adjustment method, preferably by using published quality checklists or scales. This recommendation applies to all external evidence, whether from a randomized controlled trial or observational data sources. The term “quality,” in this context, refers not only to features like data completeness and accuracy, but also extends to the confidence that the design and conduct of the data source are protected from bias.
RECOMMENDATIONS

SECTION I: WHETHER AND WHEN TO ALLOW TREATMENT SWITCHING

The decision whether or not to allow treatment switching is affected by a number of factors, including the type and stage of cancer, patients’ prognoses, availability of alternative therapies, the mechanism of action of the drug under investigation, and the type and complexity of study design, among others. Given the myriad of considerations, it is often difficult to clearly articulate precisely when allowing treatment switching is appropriate and when it is not. Nevertheless, this section identifies a few specific situations where the choice to allow or not to allow seems clear. Importantly, however, most studies will not lie at either extreme and researchers and sponsors will have to consider other factors in consultation with stakeholders. Finally, key decisions and procedural steps that should be taken if treatment switching is allowed in the study are discussed. It is important to note that “treatment switching” in this document refers to patients in the control arm switching to the experimental treatment, often but not always with late stage disease. This kind of switching is the most common type and potentially can be evaluated using a greater variety of analytical methods.

RECOMMENDATION 1: WHEN TREATMENT SWITCHING SHOULD NOT BE ALLOWED

Treatment switching should not be allowed in clinical trials in which the experimental agent has little or no intrinsic activity but is used to modulate the efficacy of other active agents.

Rationale: When the experimental agent has little or no intrinsic activity but is used to modulate other active agents, it is likely to be an ineffective treatment for control group patients whose disease has progressed. In addition to ethical concerns, there could be analytical issues if overall survival (“OS”) in switchers is adversely affected.

Implementation: Once researchers or sponsors decide not to allow treatment switching, they no longer need the recommendations in this document.

Limitations: The therapy’s mechanism of action may not be known.

RECOMMENDATION 2: WHEN TREATMENT SWITCHING SHOULD BE ALLOWED

Researchers and sponsors should allow and plan for treatment switching in the following circumstances: (1) when the experimental therapy is already available on the market where the study is taking place; (2) when a surrogate endpoint is validated and predictive of overall survival and will be ascertained during the trial; (3) when an intermediate endpoint is highly relevant to patients.

Rationale: If the experimental therapy is already available on the market, patients who experience a trigger event would be able to leave the study and obtain the “experimental” treatment through their physician as off-label use. In such cases, data that might facilitate adjusting for switching might never be collected. It would be preferable to allow the patients to access the therapy as part of the trial and to continue collecting appropriate data. A more common variation of this scenario may be when, rather than the experimental therapy, another drug with a similar mode of action is available on the market. Because the similarities and differences between the two drugs are unlikely to be well-defined, such a case should be addressed by Recommendation 3.

In the case of a validated surrogate endpoint that is predictive of OS, once the surrogate endpoint is reached, extrapolations and models should provide sufficient information about OS to satisfy decision
makers. Significant differences in intermediate endpoints that are highly relevant to patients (e.g., quality of life) can be meaningful outcomes in themselves.

**Implementation**: In all of these circumstances, researchers and sponsors should consider the rest of the recommendations in this document. Note that if the experimental therapy is available on the market and the sponsor provides it as part of the trial, then patients will potentially have financial incentives for remaining in the trial and ethical issues will need to be considered (e.g., whether the experimental treatment must be provided free of charge or whether such financial benefit would be considered coercive). In the second case, the surrogate endpoint would need to be validated for the specific cancer and stage of disease. Regarding patient-relevant outcomes, study sponsors will need to consider how they will be incorporated into the trial and into any interim analyses that are performed.

**Limitations**: In the circumstance of international trials, it is possible that the experimental therapy would be commercially available in some countries and not in others. This situation could raise ethical concerns about fairness if elements of the study (like availability of treatment switching) are different depending on one’s place of residence.

**RECOMMENDATION 3: WHEN IT IS UNCERTAIN WHETHER TO ALLOW TREATMENT SWITCHING**

In situations where it is not clear whether or not treatment switching should be allowed, researchers and sponsors should consult with patients, patient advocates, and clinicians, and also consider the views of regulators, health technology assessors, and payers in assessing its appropriateness.

**Rationale**: As mentioned above, numerous factors complicate the decision whether to allow treatment switching, not the least of which is scientific uncertainty as to whether the treatment’s potential benefits outweigh its potential harms in the particular setting. Ultimately, however, it often will be the patients and their clinicians who will make the real-world decision whether or not to switch treatments; researchers therefore need to understand these stakeholders’ perceptions of the particular clinical situation as well as their decision making process. Obtaining the perspectives of regulators and HTAs/payers will also help determine whether various study designs that do or do not incorporate treatment switching are likely to result in the sort of clinically meaningful and scientifically valid data that will make the study ethically acceptable.

**Implementation**: Section III (Stakeholder Involvement in the Study Design Process) contains recommendations on how to identify and engage appropriate patients, advocates, and clinicians. It also addresses factors to consider about consulting with regulators, HTAs, and payers.

**Limitations**: This process may result in different researchers making divergent decisions about treatment switching in what may seem like similar circumstances. Such outcomes might be due to variations in specific factual circumstances as well as differing perceptions and values of patients and clinicians.

**RECOMMENDATION 4: TREATMENT SWITCHING TRIGGER EVENT**

If treatment switching is allowed, researchers and sponsors should carefully consider and clearly define in the study protocol the trigger event that marks when patients in the control group will be allowed to switch to the experimental therapy as well as who will determine whether or not the trigger event has occurred. Treatment switching should not be allowed before that time and the
relationship between the frequency of monitoring and the trigger event should be explicitly considered. In order to preserve the possibility of using certain adjustment methods, researchers may need to define a window of time during which a patient can switch treatments, beginning with the trigger event and ending soon thereafter.

**Rationale:** The trigger event needs to be carefully considered for various reasons. For example, disease progression, which is frequently chosen as the trigger event, may not be clinically meaningful or may not be relevant for the particular therapy. Additionally, who determines the trigger event and how long the process takes can affect whether some statistical adjustment techniques can be applied, when treatment switching actually occurs, and whether appropriate data are collected. The frequency of monitoring and interim analyses also can affect the likelihood of identifying the trigger event and thus influence its meaning. Restricting treatment switching to a window of time that begins with a trigger event is not unethical when clinical equipoise exists and may be necessary in order to use a two-stage method of adjusting for switching.

**Implementation:** Trigger events can potentially be defined on either a patient level (e.g., disease progression) or on a trial level (e.g., interim analysis reveals significant quality of life gains in experimental group) and those two situations may be treated differently.

With respect to disease progression, many regulatory agencies now accept progression-free survival (“PFS”) or other surrogate measures for market approval purposes. Depending on how “progression” is defined, however, payers and HTAs may be more or less likely to assign value to study results, including those that are statistically adjusted for treatment switching, because their clinical meaning is not well-defined. For one thing, many of the criteria used to measure “progression,” including the Response Evaluation Criteria in Solid Tumors (“RECIST”) Guidelines, are not intended to be used clinically, but only in clinical trials – e.g., to help identify promising agents that should be further evaluated in RCTs. Whether relatively small increases in tumor size that can be observed with current technology are clinically meaningful should not simply be assumed. The RECIST Guidelines themselves note that, in clinical practice, many oncologists base patient management decisions not just on objective criteria like imaging results, but also on patient symptomatic criteria.

In addition, some effective drugs, including immunotherapies, angiogenesis inhibitors, and tyrosine kinase inhibitors, can cause paradoxical increases in tumor size despite response (“pseudo-progression”), because of hemorrhage, necrosis, inflammatory processes, or fluid shifts. Immunotherapies also may increase OS without increasing PFS and commenters have asserted that none of the “usual” surrogate endpoints are useful in assessing immune checkpoint inhibitors. Because of these unconventional responses, experts developed the Immune-related Response Criteria (“irRC”), which can account for responses that include, for example, new lesions or growth of existing lesions prior to shrinkage.

Another factor that needs to be considered is the frequency of observations and monitoring. The more frequent the monitoring of the disease, the more quickly any trigger events will be identified. If patients are monitored more frequently in the study than they would be in real-world clinical practice, for example, the trigger event may not correspond to any equivalent clinical point. (With the development of sampling circulating tumor cells and circulating tumor DNA in blood, or “liquid biopsies,” and testing for genetic changes in tumors that may signal development of resistance to therapy, potential trigger events could be identified even earlier in the course of disease.)
In establishing who determines whether or not the trigger event has occurred, researchers and sponsors will need to consider and perhaps balance issues such as potential risk of bias (e.g., clinicians declaring progression prematurely so patients can access experimental therapy) and the possible effects of delays in determination, which include, among other consequences, the inability to use two-stage adjustment methods that require switching to occur within a relatively short period of time, as well an increased likelihood that patients will switch treatments out of protocol and without data collection.

As explained in more depth later, some methods of adjusting for treatment switching require establishing a secondary baseline at which point patients are assumed to be at a similar stage of disease. The time of disease progression is often used as that point. Switching must occur soon after the secondary baseline in order to minimize potential bias associated with time-dependent confounding. Researchers and sponsors therefore may need to define a window of time during which treatment switching is allowed. The length of the window depends on how likely it is that relevant changes in patient characteristics will occur during that period. When the window closes, clinical equipoise still exists (as evidenced by interim analyses’ IRB-approved stopping criteria not yet being met) and treatment switching is not ethically required: patients in the control arm of the study would receive standard of care treatment, just like real world patients with the same clinical condition. Conversely, it is not ethically necessary to wait until there is convincing evidence that the benefits of the experimental therapy outweigh its risks before allowing switching during the window. The Declaration of Helsinki, for example, provides that “[i]n the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering.”

It should be noted that if the trial is stopped because of interim analysis results and control group patients are offered the opportunity to switch to the experimental treatment before reaching a patient-level trigger event, the two-stage method might not usefully be employed. If a substantial number of patients switch then, the secondary baseline established would essentially be when the study was halted – a point in time that is unrelated to disease status.

Limitations: It may be difficult to identify the best trigger event. For example, measures of disease progression that include symptoms may not be validated, and using pure clinical judgment could compromise the utility of some statistical adjustment methods (e.g., because it might be unlikely that patients will be at similar stages of disease). Additional research and development of appropriate disease progression measurement instruments may be needed.
SECTION II: KEY ANALYTICAL METHODS AND DECISION DOCUMENTATION

There is no single best method of adjusting estimates of overall survival (or of other outcomes, including safety outcomes) in all studies with treatment switching. Every approach has limitations and underlying assumptions that may or may not hold. This section discusses intention-to-treat (“ITT”) analyses and three alternative methods of adjusting for treatment switching that investigators should evaluate for each study: (a) marginal structural models with inverse probability of censoring weighting (“MSM/IPCW”); (b) two-stage methods; and (c) rank-preserving structural failure time models with $g$-estimation (“RPSFTMs”). These techniques are reviewed in Appendix 1.

In an ITT analysis, the causal effect of assignment to an experimental treatment is estimated. Typically, however, the estimate of the causal effect of the experimental treatment itself (excluding the impact of treatment switching) is of greatest interest. Although an oversimplification of the issues, the following three-tiered framework provides structure for the subsequent recommendations: (a) at low levels of treatment switching, an ITT analysis may be the preferred approach and the results from the adjustment methods can serve as sensitivity analyses; (b) at higher levels of treatment switching, one of the adjustment methods is likely to be the most valid primary analytical method provided that certain conditions are met; and (c) with extremely high levels of treatment switching, there is a high potential that neither the ITT nor any of the adjustment methods will work well. Investigators should attempt to maximize the possibility of using all four approaches if feasible, recognizing that the nature of the available data and the aims of the study may lead to one clear favored approach. Because the adjustment approaches rest on different assumptions and have varying advantages and disadvantages, a general agreement among all the estimates will tend to strengthen confidence in the results. Conversely, serious discrepancies may help identify important sources of bias in the study. Regardless of the analytical approaches chosen, investigators should document their choices and criteria before performing the analyses.

SECTION A: SELECTING ANALYTICAL ADJUSTMENT METHODS AT THE STUDY DESIGN PHASE

RECOMMENDATION 5: EXCLUDING AND CENSORING SWITCHERS

It is generally not appropriate to adjust for treatment switching either by excluding switchers from the analysis or by censoring them at the time of the switch.

Rationale: Adjusting for treatment switching by excluding switchers from the analysis or by censoring them is prone to selection bias and informative censoring. Decisions whether or not patients switch will be determined by individual clinicians and patients and are likely to be associated with patient characteristics such as good or poor prognosis. In such circumstances, switching is not random and excluding/censoring switchers will result in a systematically unrepresentative sample.

Implementation: In general, the greater the proportion of switchers, the greater the risk of bias, and naïve analytical methods such as excluding or censoring switchers should not be used in studies with significant treatment switching. If they are, however, investigation of the direction and magnitude of bias is essential and should be provided to decision makers.
RECOMMENDATION 6: INITIAL EVALUATION OF ANALYTICAL ADJUSTMENT METHODS

Clinical study sponsors and researchers should consider the following factors in evaluating analytical methods that can be used to adjust study results for treatment switching: (1) the likelihood of the method’s underlying assumptions being true, including assessment of the completeness of the list of covariates that affect relevant outcomes and also predict treatment switching; (2) the size of the anticipated treatment effect and whether it is likely to persist after the drug is discontinued; (3) the anticipated level of treatment switching; (4) the size of the study; (5) whether the control group will have an active therapy; (6) the timing of any allowed treatment switching; and (7) whether quality external data, including observational data, are available to support assumptions or to calculate counterfactual survival times (see Section II.B and Appendix 2). Although it may not be possible to decide definitively before the trial data become available what the primary analytical method should be, sponsors and researchers should have a good sense of the probabilities and be able to articulate the standards and criteria they will use to make that decision.

Rationale and Implementation: The two most important assumptions to consider are the “common treatment effect” assumption of the RPSFTM and the “no unmeasured confounders” assumption of the MSM/IPCW and two-stage methods. With respect to the common treatment effect assumption, the best assessment can be made only after the trial data are available. At the study design phase, however, researchers can and should look to external data pertaining to the drug or its class and seek expert opinions on the clinical and biological plausibility of the assumption in light of the drug’s mechanism of action. If it appears that the treatment effect is likely to be considerably reduced in switchers, the RPSFTM may not be appropriate, although subgroup and sensitivity analysis may help clarify the situation. To evaluate the assumption of no unmeasured confounders, researchers should review data from other trials in similar disease areas on covariates, including time-updated covariates, and seek clinical expert opinions from a variety of sources. The goal is to include in the models all covariates that influence the final outcome and switching. If the list of potential covariates is not robust, the MSM/IPCW and two stage methods may be subject to increased bias.

The size and persistence of the anticipated treatment effect also affect adjustment methods. If the treatment effect in the experimental group is believed to be relatively small (hazard ratio of 0.75 to 1.00), then an ITT analysis may result in the least biased estimate, although this needs to be considered in combination with other characteristics, such as the switching proportion and the reliability of the pivotal assumptions made by the adjustment methods. If the treatment effect is expected to continue after the drug is no longer given, then the RPSFTM must make additional assumptions or analyze on a treatment group basis. Understanding the drug’s mechanism of action and seeking expert opinions may be helpful if earlier studies of the drug are not available or insufficient.

A number of factors can influence the anticipated level of treatment switching, including the clinical setting, the quality of informed consent, and available data on the efficacy and risks of the experimental therapy, among other things. At low levels of treatment switching, adjustment may not be necessary and the various methods can serve as sensitivity analyses for an ITT approach. If switching is frequent, however, one of the adjustment methods may perform better than the ITT approach. At very high levels of treatment switching (≥90%), none of the methods may work very well, particularly if the study is relatively small and the common treatment effect assumption is unlikely. The MSM/IPCW method is generally more affected by higher levels of treatment switching than the RPSFTM and two-stage approach because it depends on having a sufficiently large population of non-switchers in the control group to reliably be used to represent the counterfactual survival experience of switchers.
The specification of when treatment switching is allowed is particularly important for application of the two-stage method. That method requires defining a secondary baseline associated with a specific disease-related time point (e.g., “progression”) and switching cannot occur before that time point. Additionally, switching must follow quickly after the secondary baseline in order to minimize any potential time-dependent confounding associated with the lag between the secondary baseline event and the time of switching.

Finally, if the control group receives an active treatment, the RPSFTM can be problematic. That model requires that patients be in one of two possible treatment categories: “on the experimental treatment A” or “off the experimental treatment A.” If patients in the control group are “on treatment B,” however, the category of “off the experimental treatment A” under a standard RPSFTM would include both patients on treatment B and patients receiving no treatment (e.g., after treatment failure). Combining those two groups into one category would be inappropriate if, for example, treatment B has a survival advantage compared to no treatment. The RPSFTM might still be used in these circumstances but a number of other assumptions would have to be made.

Some information that is relevant to choosing a methodology will not become known until after the clinical trial has been conducted: the proportion/number of switchers and control group patients who did not switch, for example, or the treatment effect in the experimental group. Based on consideration of the above factors, however, sponsors and researchers should be able to assess the probable strengths and weaknesses of the various methodologies as they may apply in the setting of a specific study population that has a particular disease at a certain stage. Researchers should also be able to develop transparent and explicit algorithms and criteria for determining which method will ultimately be used for the primary analysis and which ones may serve as sensitivity analyses before the analysis is started and document these algorithms and criteria in the study protocol. Section II.C addresses the recommendation of documenting such criteria before conducting the study.

**Limitations:** Additional research is needed to determine the best approach to data analysis when levels of treatment switching are extremely high. As discussed above, not all the relevant data will be available at this stage of the clinical development process.

**RECOMMENDATION 7: DESIGNING THE TRIAL TO MAXIMIZE THE USE OF POTENTIAL ADJUSTMENT METHODS**

To the extent possible, sponsors and researchers should design the clinical trial to maximize the potential of using all recommended statistical adjustment methods that may have to be used. The most important action to take in this regard is to ensure that all data relevant to adjusting for treatment switching are collected at the appropriate times.

**Rationale:** As noted previously, there are numerous factors that affect the suitability of various analytical methods. Some are beyond sponsor and researcher control, but others can be chosen and made part of the clinical trial design. By designing the trial to maximize the potential to use several analytical methods, researchers can maximize the possibility of identifying a method that will produce reliable and valid results.

**Implementation:** One of the most important steps is to ensure that all the data relevant to adjusting for treatment switching are collected at the appropriate times. All the identified covariates and potential covariates that may affect mortality that also predict treatment switching need to be collected, including at baseline, during the trial, at the time of the trigger event (most likely disease progression), at the time
of any new treatment, and following the trigger event. Investigators should develop data collection forms that reflect these key requirements. The time from the trigger event to the treatment switch needs to be documented, as do data on factors that may affect the decision whether or not to switch (e.g., patient preferences with respect to switching, clinician’s opinion on whether the patient is suitable for switching, disease stage, functional ability, degree of social support mechanisms) and data on the actual reasons patients do or do not switch.

Post-progression data can be particularly challenging to collect, especially if progression-free survival is the primary endpoint of the trial. Ensuring that the need for continuing data collection is emphasized during the informed consent process and that trial operation teams and onsite researchers understand its importance may help improve patient cooperation. Patients could also consent to allowing investigators to access their electronic health records or insurance claims data to collect post-progression data. Although expanding the range of data collected and strengthening follow-up procedures would come at a financial cost, these steps would also help maximize the potential for regulatory approval and favorable coverage decisions resulting from trials that involve treatment switching.

The content of and process for obtaining informed consent (addressed in Section IV) may also affect the number of patients who switch. If the purposes and conditions of clinical research are explained, along with what is and is not known about the experimental therapy, and how treatment switching may affect the value of the study results, in an appropriate, thorough, and balanced way, the proportion of switchers may not be as high as researchers anticipate.

What treatment the control group receives will affect the performance of some adjustment methods. Sponsors may have limited choices because of ethical requirements depending on the stage of disease and other available clinical options, but purely from a treatment switching adjusting perspective it would be analytically optimal if the control group did not receive an active treatment in order to keep the RPSFTM approach from becoming overly complex.

Deciding when treatment switching will be allowed is a critical issue (see Recommendation 4), particularly for two-stage methods. Switching needs to be confined to a relatively narrow window between the trigger event and the time of the switch if a two-stage method is to work well. Designating such a window, or even prohibiting switching entirely, is not unethical when clinical equipoise exists.\textsuperscript{5} The frequency of interim analyses and the criteria for stopping the study based on efficacy findings will also affect the likelihood of being able to use a two-stage method. In the event that the trial is stopped and control group patients are allowed to switch over to the experimental therapy en masse at a time unrelated to their disease state, a two-stage method would not be appropriate for adjustment.

The size of the study is an obvious factor that can affect the appropriateness of the analytical methods. The MSM/IPCW approach, for example, becomes problematic with small data sets, both because there are fewer non-switchers in the control group to represent switchers, and because of model convergence issues, especially if numerous potential prognostic covariates are included in the analysis. The two-stage method is also susceptible to these problems, although to a lesser extent than the MSM/IPCW method. RPSFTMs are less sensitive to small data sets than the other two adjustment methods but can still encounter difficulties if the numbers of patients and events are very small.\textsuperscript{1} Although not driven by concerns about the treatment switching, the Society of Gynecologic Oncology nevertheless states “it is advisable to power ovarian cancer trials with registration intent for OS even if PFS is a primary endpoint.”\textsuperscript{19}
Limitations: Being able to adjust for treatment switching is only one of several objectives that sponsors and investigators will have and there will be competing concerns that affect these study design considerations. Additional data collection will have financial costs that sponsors will weigh against the potential value. Additional research on the reasons that patients switch and the factors that influence their decisions is needed.

SECTION B: USE OF EVIDENCE FROM SOURCES OTHER THAN THE CLINICAL TRIAL

Data apart from those collected during the clinical trial may help to support the analytical approach used to adjust for treatment switching. Researchers, therefore, should systematically consider the potential use of data from sources other than the clinical trial, including observational data. Although external data might help substantiate other analytical goals as well (e.g., longer term data could be helpful in grounding the trajectory of extrapolations for models), this section focuses on those aspects of external data that particularly pertain to treatment switching. Recommendations concerning how to evaluate data quality more generally are provided in Appendix 2. It should be noted that the recommendations have been written assuming that potential data sources already exist. It may be possible, however, to collect relevant contemporaneous external data while the clinical trial is underway. The considerations put forth in this section would still be relevant and should be taken into account if designing such data collection.

RECOMMENDATION 8: SEARCHING FOR EXTERNAL EVIDENCE

Researchers and sponsors should systematically search for data from sources other than the clinical trial, including both randomized clinical trials and observational data, to help support analytical approaches used to adjust for treatment switching.

Rationale: Data from sources other than the clinical trial, including both randomized clinical trials and observational data, can help reinforce and guide interpretation of results from the clinical trial, particularly analytical adjustments for treatment switching. Section II.B and Appendix 2 address in more detail how to evaluate and use external data for those purposes.

Randomized controlled trials (“RCTs”) are generally considered to be the gold standard of study designs, but there is increasing recognition that observational data also can be an important source of information on safety and efficacy of therapeutics. Although discrepancies in results between RCTs and observational data have traditionally been attributed to various biases and the lack of randomization in the observational data, well-designed and adequately controlled observational studies often do produce results that are comparable to those from RCTs. Moreover, meta-analyses based on observational studies generally produce estimates of effect similar to those from meta-analyses based on RCTs. As a result, a growing number of researchers contend that appropriate observational and real world data must be integrated into systematic reviews if an evidence-based approach is to be used. The Cochrane Collaboration, for example, has recognized this trend and developed a tool specifically for assessing the risk of bias in nonrandomized trials, and participants in a recent Institute of Medicine workshop stressed the importance of observational studies as “a component of a robust clinical research enterprise.” It follows that in interpreting studies with a substantial degree of treatment switching, appropriate external evidence can include not only RCTs but also observational data.
**Implementation:** To identify potential external data sources, sponsors and researchers should take the following steps:

- Review the published literature
- Identify and review clinical study registries such as ClinicalTrials.gov and the NIH database of clinical studies
- Review patient-oriented clinical trial listing services such as CenterWatch
- Review commercially available databases, including compilations of administrative claims and of electronic health records
- Identify and review government/public research databases
- Consider lists of registries such as the Registry of Patient Registries maintained by the Agency for Healthcare Research and Quality

Sponsors and researchers can then contact the owners or proprietors of the data to discuss access to the data as needed.

**Limitations:** Not all relevant data will be published or otherwise publicly available. Issues such as protecting patient privacy and concerns about safeguarding intellectual property and research opportunities may hinder efforts to obtain access to data.

**RECOMMENDATION 9: FITNESS OF EXTERNAL EVIDENCE**

Clinical study sponsors and researchers should assess external data and data sources they are considering using to support their chosen analytical adjustment method in order to be sure that the data are fit for their intended use.

**Rationale:** The “fitness for use” of data is a concept very closely related to data quality. As the Data Quality Collaborative has explained, data quality is context-dependent — a given data element or source may be high quality for one use and poor quality for a different use. The reliability and validity of a database are not static characteristics, but can vary considerably depending on the questions asked and the analyses performed. To be considered fit for use, the data must be able to adequately answer the specific study question.

Most observers would agree, for example, that the National Cancer Institute’s Surveillance, Epidemiology, and End Results (“SEER”) registry is a premier source of cancer information in the US. It is extensively audited for both accuracy and completeness. At the same time, however, it can lack depth of data – for instance, tumor stages are not always specified by tumor/node/metastasis criteria, surgical margin status is often not available, and comorbidities are not included. If those data elements are critical to the research question, the SEER registry may not be a fit data source in spite of its high quality.

Basing analyses on data that do not fit adequately with the inquiry being undertaken can lead to potentially incorrect conclusions. One study that applied the same study design to several observational databases that differed in terms of covered populations, data capture completeness, and recorded information accuracy, among other factors, resulted in widely disparate findings, including both statistically significant positive results and statistically significant negative results for the same research question. Similarly, two different studies examining the same research question and using the same database can still reach opposing conclusions, perhaps because of differences in definitions, eligibility criteria, and study design.
Implementation: The most important specific factors to consider in assessing the fitness of data sources will vary with the purpose of using the external data. Elements particularly relevant to uses of data to support analyses in the context of treatment switching (e.g., to calculate counterfactual survival or to demonstrate the validity of a surrogate outcome measure) are addressed in more detail in the text following Recommendation 10. In general, however, one should consider the following factors when assessing fitness:

- definition of the disease
- stage of the disease
- eligibility/inclusion criteria for population
- similarity of populations
- definition of the intervention
- outcome definitions (e.g., is “progression” defined similarly?)
- duration of data
- available and recorded important covariates
- time period during which data were collected

Ideally these factors would be the same across data sources, but even if they are not it may be possible to modify the external data to replicate relevant criteria. For example, one could exclude patients with stage IIIA or lower cancer from an external dataset if planning to apply the analytical results to a study of patients with advanced disease.

Limitations: It is probably unlikely that the available external data will fit their intended use perfectly. Reviewing decision makers will have to decide how well the analytical results from the external data represent the expected results of the clinical trial with treatment switching. This judgment is difficult to make quantitatively but can be made qualitatively based on the criteria in this section. If external data are at the patient level, however, it may be possible to adjust for differences in patient characteristics.

RECOMMENDATION 10: USES OF EXTERNAL EVIDENCE
When feasible, researchers should integrate appropriate external data with data from a clinical trial that includes treatment switching for the following purposes: (1) predicting counterfactual survival times in patients who switch; (2) examining treatment switching adjustment methodology assumptions; and (3) evaluating the relationship between overall survival and earlier surrogate endpoints (e.g., objective response rate or progression-free survival).

Rationale: Data from sources outside the clinical trial can provide important perspectives on the adjustments for treatment switching by allowing comparison between the study results and other information about the disease and its treatment. For example, if estimated counterfactual survival times in the study are substantially different from those documented in the literature, the discrepancy may indicate problems with the adjustment method and further exploration may be needed. Conversely, consistency between the estimates and the literature can provide support for the adjustment method.

Implementation: This section describes the types of analyses to perform for each main use. As discussed elsewhere, patient selection criteria should match between the clinical trial with treatment switching and the individuals selected from the external data, as should any relevant definitions of terms such as “progression.” It is also important to emphasize that research in the area of incorporating external
evidence into clinical trial analyses is ongoing and researchers should keep abreast of recent developments.

**Counterfactual Survival Times**
Both two-stage adjustments and RPSFTMs estimate counterfactual survival times for patients who switch, based on the actual observed clinical trial data. To instead use external data to predict counterfactual survival in that group, one needs (a) outcome data, in this case overall survival, in the external dataset, and (b) patient covariates in both the external dataset and clinical trial that are prognostic for outcome. In one study of patients with advanced multiple myeloma, for example, patient variables considered as predictors of OS included age, gender, Durie-Salmon disease stage, presence of lytic bone lesions, performance status, maximum response, and M-protein and beta-2 microglobulin levels both at start of first line and at progression with each treatment.41

In general, the number and importance of the covariates available greatly affect the quality of the estimates of counterfactual survival. Potential covariates should be designated *a priori* and might be identified through, e.g., literature searches and/or expert opinion. If a potential covariate is available only in one of the external data source and the clinical trial, then sensitivity analyses should be conducted to explore the influence of the covariate on the analyses.41,44

The two best analytical approaches in this context are (1) using prognostic covariates to match clinical trial patients who switched with patients in the external dataset, and (2) developing a predictive model for survival time (with or without a Bayesian framework) based on the external dataset and applying it to the control group patients who switched. Additional research is needed to help identify the advantages and disadvantages of different analytical approaches in various circumstances. Until best methods are identified, either a matching or a predictive model approach (or both) may be used.

(Simply comparing survival statistics from an external dataset with a population similar to that in the study used for the adjustment methods’ estimates might be a “bare minimum but better than nothing” approach.)

In order to validate the matching algorithm or predictive model, it should be developed based solely on the external data and then applied to the patients in the control group who did not switch. If the predicted overall survival generated by the algorithm or model for those patients closely agrees with the actual observed overall survival, decision makers should have greater confidence in the counterfactual survival times calculated for the switching patients.

**Adjustment Methodology Assumptions**
RPSFTMs rely on the assumption of a common treatment effect, meaning that no matter when in the course of disease the treatment is given it has the same effect (relative to the length of time it was taken for).13 Because control patients who switch treatments usually do so at the time of disease progression, they receive the experimental drug later in the course of their disease than the patients initially assigned to the treatment group (who had not progressed when they started the experimental drug) and may not experience the same effect. RPSFTMs that have relaxed the common treatment effect assumption, regardless of their complexity, have not been successful.45–47 Therefore, if appropriate external data (information on the experimental treatment’s effect by disease stage or time since diagnosis, for example) are available, analyses should be performed to determine whether or not the assumption of a common treatment effect is credible.
Marginal structural models with inverse probability of censoring weights and two-stage models both rely on the assumption that there is no unmeasured confounding. Although it is not possible to prove that this assumption holds, there may be supportive steps to take to bolster its credibility. One step is to be completely transparent about the covariates and confounders considered, the criteria for their selection, and the available information supporting their use. Additionally, if an appropriate external data source has measured more or different prognostic covariates than the clinical trial, then the external data should be analyzed to determine whether or not those covariates were important predictors of overall survival in the external data source. If the additional or different prognostic covariates are not important predictors, greater weight may be given to the adjustment for treatment switching. Researchers may also gain insight into the assumption by identifying prognostic characteristics in similar disease areas.

Relationship Between Overall Survival and Earlier Surrogate Endpoints
If appropriate and sufficient external data are available to assess the relationship between overall survival and earlier surrogate endpoints, they should be analyzed to see whether uncertainty about the clinical trial overall survival outcomes can be reduced. The relationship would need to be assessed for the particular type of cancer and for the same stage that was studied in the clinical trial that involved treatment switching. It is also possible that a relationship observed between a surrogate endpoint and overall survival is specific to the particular treatment and cannot be generalized to different agents.

Limitations: The limitations noted for the other recommendations in this section also apply to this one. Specifically, not all desired data will be published or publicly available, the data that are available may not fit their intended use well, and it will be difficult to assess how well the analytical results represent the expected results of the clinical trial with treatment switching.

SECTION C: DECISION DOCUMENTATION

RECOMMENDATION 11: CONTENTS OF PROTOCOL AND STATISTICAL ANALYSIS PLAN
Investigators should document in the protocol the key decisions and procedures relating to treatment switching, as well as their underlying rationales. Fundamental topics that should be addressed (if applicable) include: whether or not treatment switching will be allowed during the trial and why; the conditions or times when treatment switching will be allowed and why; any trigger event chosen and why (including the study’s definition of “progression” if that is a trigger event); whether there will be any additional costs to patients if they switch and why; what external evidence investigators will examine, what analyses will be performed on it, and how the results will be used; and what data relevant to treatment switching will be collected at which times, how long data collection will continue, and why.

Investigators should also identify either in the protocol or in the statistical analysis plan (“SAP”) the most likely appropriate statistical analysis methods (evaluated as described in Section II.A) and state how each method will be analyzed at the conclusion of the trial, following a six-step process to determine its suitability (see Recommendation 12). The investigator should set forth the criteria for selecting the primary methodology, identifying which other methodologies should be applied for purposes of comparing results for consistency, and what other sensitivity analyses will be performed. Any external data sources to be examined and their uses should also be documented a priori.
The SAP should provide more technical and detailed explanations of the procedures that will be followed to execute the analyses above. While the demarcation between the information that should be in the protocol and the information that should be in the SAP is not always distinct, in general, the protocol should set forth what analyses will be performed and why, while the SAP sets forth details about how the analyses will be performed.

**Rationale:** The documentation of and reasoning behind the key treatment switching and study design decisions need to be clearly set forth in the protocol in order to avoid ambiguity, foster transparency, and provide information for study personnel, ethical review boards, and other stakeholders. The analyses that are performed, the process and criteria for selecting the primary methodology, and, ultimately, the study results, will enjoy greater acceptance and be more credible if they are stated *a priori*. Otherwise, any analyses or adjustments may appear to be *post hoc* and chosen to place the experimental therapy in the best light possible. Decision makers may be reluctant to accept any adjustment method as a primary analytical approach absent these *a priori* specifications. As the International Conference on Harmonisation has put it, “*only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.*”

Because investigators will be unable to confidently conclude at the design stage which analytical method will ultimately prove to be the best to use at the end of the study, the protocol should describe the underlying assumptions of each method and the checks on them that will be performed. It should also set forth the criteria for selecting the best methodology, identifying which other methodologies should be applied for purposes of comparing results for consistency, and what sensitivity analyses will be performed.\(^\text{18}\)

**Implementation:** The goal of this recommendation is to achieve transparency about how critical decisions were or will be made and it should be applied in that light. It ultimately makes little difference whether the needed information is placed in the protocol or in the SAP, so long as it appears in one or the other, the appropriate stakeholders have access to it, and any changes in the plans are documented and explained. It may be useful to note in the protocol that there continues to be emerging research on analytical methods that could affect the stated plans.

If any planned analyses, like sensitivity analyses, will require extra data collection, even for a subset of the randomized patients, then the protocol should state this and include provisions for collecting these data. If computer simulation will be needed, then the protocol should give details about what will be simulated, how the simulations will be carried out, etc.

**Limitations:** Amending study protocols is often a cumbersome and expensive process.

**SECTION D: FINAL ANALYTICAL METHOD SELECTION AND REPORTING**

**RECOMMENDATION 12: FINAL SELECTION OF ANALYTICAL METHODS**

When clinical trial data become available at the conclusion of the study, investigators should follow a six-step process to assess which analytical methods are appropriate: (1) conduct an initial screen; (2) assess the number and proportion of switchers and non-switchers in the control group; (3) assess the key assumptions; (4) examine the output and performance of the methods; (5) perform extrapolation if needed; (6) review sensitivity analyses and any information from external data.
Best Practices for the Design, Implementation, Analysis, and Reporting of Oncology Trials with High Rates of Treatment Switching

[NOTE: This recommendation is based on the process set forth by Latimer N, Abrams K, Lambert PC, et al. in 2014.13]

Rationale: Some key information that is important in selecting an analytical method will not be known until the clinical trial data become available. At that point, investigators should be able to develop the remaining information and utilize a stepwise structured process to determine the best primary analytical method.

Implementation: The process and criteria that are used to select the primary analytical method should have been documented in the protocol and statistical analysis plan a priori. Implementation then consists of adhering to the processes and applying the criteria in those documents. As stated in Section II.C, the a priori plan should have been consistent with this six-step process.

Step 1: Conduct an initial screen. Determine whether appropriate and sufficient covariate data were, in fact, collected. Determine when treatment switching occurred (only after a disease-related time-point and only during a short time afterwards?). Did the control group involve an active comparator?

Step 2: Assess the extent of treatment switching. If more than 90% of the control group switched, the MSM/IPCW approach is prone to bias and high uncertainty (assuming a total sample size of around 500, or 250 per arm, ≤10% non-switchers left in control group is ≤25 persons). In that case, randomization-based methods (RPSFTM) should be preferred unless (a) the control is an active comparator, or (b) there is strong evidence against the common treatment effect assumption. If less than [X]% of the control group switched, the ITT method will most likely provide the best results and the other methods can potentially serve as sensitivity analyses.

Step 3: Assess the key assumptions. Although it is not possible to be sure that the “no unmeasured confounders” assumption holds, investigators should confirm that other trials and similar disease areas were examined to identify potential covariates and that relevant experts were surveyed. If they were not, the investigators should review those sources to determine whether any likely prognostic characteristics were omitted. The investigators should then consider the data collection -- was it stopped at any point? Data must be constantly collected, including after progression, for optimal application of the MSM/IPCW approach. Are the right covariates available at the secondary baseline? (This is important for two-stage methods.)

With respect to examining the “common treatment effect” assumption, the following steps should be taken:

- Attempt to compare the treatment effect in switchers with that in the experimental group (e.g., by comparing survival times and response rates), recognizing that these simple analyses are prone to bias; consider performing analyses based on an earlier cutoff (and thus with a smaller percentage of switchers) to determine whether the acceleration factor based on the full data changes
- Analyze the time from randomization to switch because if important disease events did not occur prior to switch the common treatment effect assumption may be more plausible
- If the trial involved patients with different stages of disease or who had received different numbers of previous lines of therapy, investigate the treatment effect in those subgroups, recognizing that switching may lead to bias

Finally, although not strictly related to the common treatment effect assumption, the persistence of the
treatment effect should be examined and if it is likely to continue after treatment discontinuation, then a “treatment group” application of the RPSFTM algorithm should be considered.¹

Step 4: Review the output of the various methods to assess whether they likely performed well. General steps investigators should take include:

- For the RPSFTM, assessing whether the g-estimation procedure has successfully and appropriately determined a single estimate of the treatment effect
- For the IPCW and two-stage methods, assessing the fit of the models used and whether or not they have converged
- Evaluating whether the adjusted estimates make sense, perhaps with respect to estimates from other studies or by an assessment by experts on likely treatment effects. External data can help validate that the control arm estimates are reasonable (regardless of the method applied)

Investigators should also undertake the following steps that are specific to particular analytical methods:

For RPSFTMs: (a) consider the degree of recensoring, which is necessary to avoid informative censoring and results in the loss of longer term survival information; (b) assess the sensitivity of the results to the choice of RPSFTM – for instance the “on treatment” RPSFTM compared to the “treatment group” RPSFTM; (c) assess the g-estimation output to see whether the method has identified a unique treatment effect that results in equal counterfactual survival time between the randomized groups; (d) assess whether the untreated counterfactual Kaplan-Meier curves derived for each treatment group do indeed suggest similar untreated survival times.

For an MSM/IPCW approach, assess the weights assigned to each patient over time to see whether any patients were allocated particularly high weights and whether weighting models successfully converge.

For a two-stage method: (a) consider the degree of recensoring; (b) evaluate the common treatment effect assumption by examining whether the treatment effect estimated for switching patients is similar to that estimated for patients initially assigned to the experimental arm; (c) assess whether the results are sensitive to the type of accelerated failure time model used to estimate the treatment effect in switchers; (d) consider a plot of “time to switch” from the secondary baseline.

The ITT approach may present the least bias if the three adjustment methods above are unlikely to have performed well. It may be appropriate to use when (all else being equal): (a) switching proportions are low, and/or (b) the treatment effect is believed to be small (hazard ratio of around 0.75 to 1.00 for the experimental group, although note the hazard ratio is difficult to be certain of in the presence of treatment switching), and/or (c) the treatment effect is likely to be much reduced in switchers compared to the experimental group.

Step 5: Undertake extrapolation of survival data based on the statistical outputs of the various adjustment methodologies, following the recommendations of Latimer (2013).³⁰

Step 6: Review sensitivity analyses and results from external data analyses. These analyses may help to reinforce the results from the adjustments or demonstrate the uncertainty associated with each method. Although not required, a sensitivity analysis of different definitions of “progression” might be informative. The foundation for such analyses would have to be laid earlier in order for appropriate data to be available.
Limitations: The study must have been properly designed and executed in order to implement this recommendation.

RECOMMENDATION 13: REPORTING SELECTION OF ANALYTICAL METHODS AND RESULTS
The results of the final selected primary analytical method should be provided to reviewing regulators, HTA entities, and payers, along with all justifications for the method’s selection, supporting and opposing evidence, uncertainties identified, and an assessment of how well it worked. Fundamental data that should be provided regardless of adjustment method used (if any) include baseline characteristics for switchers and non-switchers, information on who switched over time, and measures of switching both as percentage of patients who switched and the amount of exposure and follow-up time they contributed. The results of the ITT analysis should always be provided to reviewers. All other methods considered by the investigators should be reported and discussed as well. If any analyses were performed using those methods, the results should be provided; if any of the key alternative adjustment methods were ruled out, the rationales must be supplied. The degree of detail provided about the analyses must be sufficient to allow reviewers to clearly understand what specific analyses were undertaken and the methodology employed. Similar standards for the reporting of analytical methods and results in the medical literature also need to be developed to provide transparency and consistency.

Rationale: The results of the ITT analysis should always be provided: it is a valid test of the null hypothesis, maintains the original randomization, uses data from all randomized patients, and reflects the design and conduct of the study. Decision makers also need to be able to assess the rationales and support for the choice of the primary analysis method and to place it in the context of the other options available. Too often, decision makers have been provided with results from a single adjustment method with no explanation, no discussion of how well the method worked, and no mention of any other analyses using other methodologies.

It should be noted that the same observations frequently hold with respect to studies that are published in the medical literature. Features of the analytical approach that are provided can vary significantly from study to study and are often insufficient to allow readers to accurately assess the study results. Reporting standards for medical publication must be adopted for greater transparency of methods and comparability of clinical trials involving treatment switching. While developing these standards is beyond the scope of this document, reports at a minimum should provide information on the extent of treatment switching in terms of patient numbers and ideally with respect to timing. They should also discuss the potential impact of treatment switching, ideally through the analytical methods described in this guidance. We strongly recommend that journal editors seek consistency in the way the results of these studies are reported.

Implementation: The recommendation is straightforward. Its essence is that sponsors should address the ITT analysis and all three (at this time) principal adjustment methods in the submissions they make to key decision makers. If the investigators did not employ a particular method, they must offer a justification demonstrating that the approach would have been inappropriate. If data that would facilitate application of a methodology could have been collected during the trial but were not, the omission must be explained. Similarly, if the study design foreclosed use of one of the key adjustment methods, the rationale should be provided. (NOTE: Recommendation 14 addresses how analyses of external evidence should be reported to decision makers.)

In the case that the investigators choose to apply an adjustment method other than the one that would
result from following the protocol (e.g., a new adjustment method is developed), the investigators should document the change and the reason for it to avoid the appearance that the change came about because the results of the originally planned adjustment method were unfavorable.

**Limitations:** Many of the recommendations require a level of statistical sophistication on the part of sponsors and reviewers that may not presently exist. In addition to the information provided here, however, there is a not insubstantial published literature available to stakeholders that can provide more substantive detailed guidance than this document can impart. A learning curve on the part of virtually all stakeholders can be expected along with the possibility of frustrating mismatches between the expertise of various stakeholders.

**RECOMMENDATION 14: REPORTING ANALYSES OF EXTERNAL EVIDENCE TO DECISION MAKERS**

Along with any analyses of external evidence that they provide to decision makers, clinical study sponsors and researchers should include: (1) their assessments of the external data quality and fitness; (2) brief information on external data sources they considered but did not select along with an explanation of the decision; (3) results of all analyses conducted; (4) results of sensitivity analyses and, when appropriate, model validation; and (5) their *a priori* specification of the data source to be used or the criteria to be used for its selection and the analyses to be performed. Any analyses performed that were not specified *a priori* should be clearly identified.

**Rationale:** Decision makers need to be able to assess the quality and fitness of external data, particularly observational data, in deciding what weight to give analyses of those data. Providing assessments of the quality and fitness of the data will assist decision makers with that process, both by providing assurance of the data quality and by alerting decision makers to any potential problems with the analyses based on those data. Furnishing information about who collected the data, how, why, from whom, and whether and how they were quality checked, for example, allows decision makers to assess for themselves the quality of the data and better evaluate the strengths and limitations of the analyses. Providing the results from all analyses performed, including sensitivity analyses and model validation outcomes, accomplishes a similar goal. Additionally, being able to compare results (e.g., adjusted and unadjusted) is important to the weight that decision makers may give an analysis. If results can be shown to be consistent through sensitivity analyses and across relevant patient subgroups, as well as in different datasets, the strength of analytical results can be reinforced.

**Implementation:** Implementation of this recommendation is relatively straightforward. If researchers submit an analysis of external data to a decision maker, they need to include:

- an assessment of the quality of the data and data source
• an assessment of the fitness of the data for the analysis
• the results of all analyses conducted on the data (e.g., adjusted and unadjusted)
• a description of any external data sources considered for use but not selected and the reasons why
• a copy of an *a priori* research plan that includes:
  o definition of the population from the external data that will be used
  o primary and secondary outcomes (as appropriate)
  o data source(s) to be used or criteria for their selection
  o database extraction and statistical analysis plan
  o possible confounders and covariables to be considered
  o the sensitivity analyses and model validation to be performed

As part of the process of identifying data sources and planned analyses *a priori*, researchers should also specify whether the results will be used (a) to support the adjustments for treatment switching in the clinical trial (e.g., by supporting underlying assumptions or providing an additional estimate of a result) or (b) as an alternative to the analysis based on the data from the clinical trial in which treatment switching occurred. The recommendations apply equally in both situations; the important point is to state the use of the analysis before performing it in order to avoid any appearance of selective designation.

One set of useful resources for both researchers and reviewers is a series of papers developed by the International Society for Pharmacoeconomic and Outcomes Research (“ISPOR”) that address good research practices for retrospective database analysis, including approaches to mitigate bias and confounding in the design of non-randomized studies. ISPOR has also set forth a 27 question checklist to help decision makers evaluate the quality of retrospective databases and their suitability for the particular research questions, among other things. Researchers can likewise use such checklists to guide their study designs and reports to decision makers. Other valuable guidance can be found in the Strengthening the Reporting of Observational Studies in Epidemiology (“STROBE”) Initiative’s checklist of items that ideally should be addressed in reports of observational studies, the NICE Decision Support Unit Technical Support Document 17 on use of observational data to inform estimates of treatment effectiveness, and a validated checklist from the GRACE Initiative for evaluating the quality of observational cohort studies for decision-making support.

**Limitations:** The various checklists mentioned above were developed for reasons other than to evaluate the relevance of particular datasets for assessing treatment effects in the presence of treatment switching. Not every item will necessarily be appropriate or applicable.
SECTION III: STAKEHOLDER INVOLVEMENT IN THE STUDY DESIGN PROCESS

Benefits accrue to both researchers and stakeholders when stakeholders are engaged in the drug development process. This section makes recommendations for involving three different types of stakeholders: patients and clinicians; ethical review boards; and those not directly affected by the study but who have substantial interest in the results, such as regulators, health technology assessors, and payers.

RECOMMENDATION 15: DIRECTLY AFFECTED STAKEHOLDERS: PATIENTS AND CLINICIANS

Study sponsors and researchers should involve stakeholders who may be directly affected by treatment switching, such as patients and clinicians, in the clinical trial design and development processes relating to treatment switching. Stakeholder involvement should begin with the trial conceptual stage and continue throughout the trial with respect to any potential change in protocol or study design that involves treatment switching.

Rationale: Patients and patient advocates can contribute in important ways to the study design process. For example, they can: provide perspective on their disease, unmet needs, burdens, and other factors related to their decision making about treatment selection and switching; help develop key concepts such as the best definition of “progression” to use; identify burdensome or otherwise unrealistic data collection processes or study visit schedules; and help develop patient education materials and informed consent substance and processes, among other things. Clinicians, including, in particular, community oncologists and oncology nurses (who manage the majority of patients who are participating in oncology drug trials) are key resources and clinical decision makers who will certainly be involved in treatment switching determinations. Their involvement can help identify significant clinical decision points, provide insight into how treatment switching decisions are made, and offer additional perspectives on study requirements, burdens, and barriers.

If these key stakeholders are not involved from the conceptual stages of the trial, sponsors and researchers can waste valuable resources and time by, for example: defining outcomes that are not relevant to decisions about treatment switching; establishing unrealistic or unworkable schedules and processes such that critical data needed for statistical adjustments are not collected; and drafting documents and materials that are inappropriate or ineffective in explaining treatment switching and clinical options.

Implementation: Researchers can identify potential patients and advocates through a number of possible sources, including national advocacy groups, on-line and social media patient communities, institutional support groups, grant committees, and patient representatives on various government committees, among others. In assessing the suitability of patient groups, researchers should consider factors such as the group’s history, experience, expertise, mission, priorities, relationships, programs, and whether they are involved with cancer generally or with the specific disease being studied. The Clinical Trials Transformation Initiative has developed detailed and useful recommendations on Effective Engagement with Patient Groups around Clinical Trials that may be helpful in this undertaking. In assessing individuals, researchers should strive for people who provide representational as opposed to idiosyncratic views. The number of patients and advocates involved needs to be sufficient to provide a broad range of views and should reflect the diversity of the relevant patient population to the extent possible. Sources for identifying community oncologists and oncology nurses include: at the study sites...
under consideration; through professional organizations such as the Community Oncology Alliance; and on government or grant committees.

Key relevant study design topics on which patients and clinicians should be consulted include:

- Whether or not treatment switching will be allowed
- When treatment switching will be allowed
- The process to follow to implement treatment switching
- How to define “progression” and other key terms
- Type, timing, and feasibility of data collection
- Timing of interim analyses and criteria for stopping the trial

Although some key issues may be unique to a particular trial, many of these topics may pertain more broadly to a group of patients with a particular disease at a particular stage or to a particular class of drug. The available treatment options, for example, or what the usual clinical trigger for changing therapies is, would likely be the same for patients across a country or for drugs within a class. Thus, there may be opportunities for pre-competitive discussions among sponsors and stakeholders to try to resolve generally applicable issues.

Limitations: There are costs associated with this recommendation including those associated with identification of appropriate representatives, communication, travel, and people’s time. Stakeholder involvement in the study design process also will likely increase the length of time needed, at least initially. While many of these costs will likely fall on sponsors, some patient or clinician advocacy groups may have the resources and mission to be able to contribute in some capacity. Importantly, there may be regulatory, legal, or other constraints on the interactions study sponsors can engage in with patients and clinicians. Payments to individuals sitting on study committees or otherwise advising the sponsor or to their organizations could potentially raise issues of conflicts of interest and should be carefully considered.

RECOMMENDATION 16: ETHICAL REVIEW BOARDS

Entities such as Institutional Review Boards or Research Ethics Committees that conduct ethical reviews of proposed trials should require study sponsors and researchers to include patients and clinicians in the study design processes relevant to treatment switching, beginning with the trial conceptual stage. They also need to assure themselves that the trial design and analysis plans relating to treatment switching will allow valid and robust answers to be derived for the trial questions posed.

Rationale: Ethical review boards (“ERBs”) are charged with assuring that the rights and welfare of humans participating as research participants are protected. Many of the treatment switching issues decided during the study design process directly pertain to patients’ rights; e.g., whether or not treatment switching is allowed, under what circumstances, and when. Involving patients and other affected stakeholders in the design process provides greater opportunity for the patient voice to shape the study in a way that more fully accounts for patient interests. By explicitly requiring study sponsors to include patients and clinicians in the study design process, ERBs can better protect patients and help achieve rapid conformance with this standard.

In addition, clinical studies must have social value and scientific validity, among other attributes, in order to be considered ethical. If a study imposes on participants particular conditions, visits, data
collection procedures, etc. that are related to treatment switching, those procedures need to be scientifically appropriate and contribute to the ability to derive answers. ERBs therefore need to assure themselves that the trial design and analysis plans relating to treatment switching result in an ethically-acceptable study.

**Implementation**: ERBs generally have publicly available policies and guidances, as well as application/submission forms. They should revise applicable statements and documents to clearly require sponsors of oncology drug trials involving treatment switching to include patient and clinician representatives in the study design processes relevant to treatment switching and to provide the board with specific information about their involvement.

**Limitations**: ERBs are often not directly consulted until the end of the clinical study design process, making it critical that ERBs amend available policies and guidances in order to provide notice to study sponsors of requirements. If study sponsors fail to consult ERB procedures and requirements early in the design process, they may encounter significant delays in beginning clinical trials.

In some geographic regions, researchers have a choice of ERBs. While the ERBs apply the same general standards, their interpretations and requirements may differ. If this recommendation is not universally adopted by the relevant ERBs, researchers may be able to “opt out” by selecting an ERB that does not require stakeholder involvement. Additionally, some ERBs may not have the technical expertise or the time to delve deeply into the technical aspects of treatment switching.

**RECOMMENDATION 17: REGULATORS, HEALTH TECHNOLOGY ASSESSORS, AND PAYERS**

Stakeholders such as regulators, health technology assessors, and payers, who are not directly affected by treatment switching but who have substantial interest in the study results and whose interpretations of those results will directly affect market or patient access, should be receptive to requests from study sponsors and researchers to discuss issues about treatment switching. Appropriate topics include (a) the stakeholder's position on the recommendations in this document on the design and analysis of trials in which treatment switching is expected, (b) aspects of treatment switching that this document does not address, and (c) uncommonly challenging situations concerning treatment switching.

**Rationale**: Regulators, HTA agencies, and payers vary in their evidentiary requirements, how they regard treatment switching and statistical adjustment methods, and the associated implications for potential approaches to treatment switching. Study designs, endpoints, and analytical plans that meet the requirements of one stakeholder or class of stakeholders may not satisfy another. The recommendations set forth in this document are intended to delineate a common ground on most issues associated with treatment switching. Nevertheless, there will be situations in which researchers will need additional guidance in order to meet stakeholder requirements. Open and honest dialogues between stakeholders, study sponsors, and researchers may thus be needed to clarify positions, avoid wasting resources, and ensure that trials meet the needs of key decision makers so that patients gain appropriate access to promising new treatments.

**Implementation**: Study sponsor and researcher discussions with regulators, HTA bodies, and payers, could be expedited if they were centered around the recommendations in this document and if regulators, HTA bodies, and payers made clear in advance their position with respect to these recommendations (e.g., through guidance documents or policy statements). In such circumstances, routine meetings between reviewing stakeholders and study sponsors to discuss treatment switching
may often not be needed. In the absence of clarity, however, reviewing stakeholders should be receptive to requests from study sponsors and researchers to meet to consider the challenges posed by treatment switching and how best to design studies to meet stakeholder expectations. Additionally, reviewing stakeholders need to be open to exceptional situations where more extensive consultation would be constructive.

Where regulators, HTA bodies, and payers have established mechanisms for engaging with study sponsors and researchers, they should be used. In particular, mechanisms for joint scientific dialogue should be used to allow direct discussion between and with stakeholders about potentially differing views of study design and evidentiary expectations.

**Limitations:** Some regulators, HTA bodies, and payers may have legal constraints or other limitations on their ability to meet with individual sponsors. In these situations, it is particularly important for the stakeholder to make known its views on the recommendations in this document and its preferred approaches for studies with a high degree of treatment switching, whether through guidance documents and policy statements or less formal mechanisms.
SECTION IV: INFORMED CONSENT: PROCESS AND CONTENT

It is important to consider that randomized clinical trials of new oncology drugs are usually conducted first in patients who have late-stage disease and no or poor treatment options — and this is often the setting for treatment switching. Patients with late-stage cancer are often considered to be a particularly vulnerable population\(^6\): the disease setting and other factors may make such patients more likely to make healthcare decisions and decisions about participation in clinical trials out of desperation rather than based on considered reflection. One critical implication of this perception is that informed consent in this setting needs to be thorough and non-coercive. To help achieve those goals, this section sets forth two recommendations that address the informed consent process and one recommendation that pertains to informed consent content.

RECOMMENDATION 18: INFORMED CONSENT PROCESS: TWO CRITICAL STAGES
Clinicians responsible for obtaining informed consent should be particularly sure to provide key information about treatment switching at two critical times: (1) when patients are considering whether to enter the trial, and (2) when they are considering switching treatments.

Rationale: Informed consent in a clinical trial is best regarded as a continuous process, not an event. As the Council for International Organizations of Medical Sciences’ International Ethical Guidelines for Biomedical Research make clear, for example, informed consent begins when initial contact is made with a prospective participant about entering a study and continues throughout the course of the trial.\(^5\) Researchers’ obligations to provide relevant information extend to critical decision points during the trial, including at the time of any disease progression or other trigger for consideration of treatment switching. Those two decisions — whether to enter the trial and whether to switch treatments — are the most significant for both patients and the trial results.

Implementation: In considering who should provide information to a patient who is considering entering a clinical trial, it is important for clinicians to keep in mind the possibility of conflicts of interest. The American Medical Association’s Council on Ethical and Judicial Affairs advises as follows:

> When a physician has treated or continues to treat a patient who is eligible to enroll as a [participant] in a clinical trial that the physician is conducting, the informed consent process must differentiate between the physician’s roles as clinician and investigator. This is best achieved when someone other than the treating physician obtains the participant’s informed consent to participate in the trial.\(^6\)

In addition, physicians may not have sufficient time to provide patients with all essential information, ensure that the patients understand it, and answer all questions. They also may not know all the complexities involved with statistical adjustments for treatment switching. Research sponsors and researchers therefore should strongly consider (1) involving other professionals, such as nurses or other clinical study personnel, in the informed consent process for entering the trial, and (2) developing high quality educational materials for patients, and perhaps for clinicians, regarding treatment switching as well as providing clinicians with information on effective ways to use them.
At the time of disease progression or other trigger for switching treatments, it will likely be the patient’s treating oncologist who will review all the treatment options, including switching, and explain how treatment switching might affect them. Again, sponsors would be well advised to provide educational materials for patients and clinicians for this phase of the study.

Limitations: Treatment switching is complicated and patients should be provided as much time as they need to consider their participation in the trial. Full understanding is unlikely to be accomplished in a single session.

RECOMMENDATION 19: INFORMED CONSENT PROCESS: DRAFTING THE CONSENT FORM

Researchers should involve patients and/or patient advocates in drafting the consent form language regarding treatment switching.

Rationale: Patient and/or advocate involvement will help ensure that the information about treatment switching that is most relevant to potential study participants is included and that the language is understandable.

Implementation: Section III of this document (Stakeholder Involvement in the Study Design Process) provides information about how to identify appropriate patients and advocates. Ideally, researchers would include some people with clinical trial experience involving treatment switching and some people without such experience. Patient representatives need to be involved from the beginning of the drafting process, first helping to confirm or identify the most important aspects of treatment switching to convey and then advising on how to convey them. It is not sufficient for researchers to independently draft consent form language regarding treatment switching and then provide it to patients and advocates for comments.

Limitations: There is no single “patient viewpoint.” Rather, there are multiple patient viewpoints that will be difficult, if not impossible, to capture completely. Researchers should strive to engage diverse patients and advocates but they do not need to try to include every possible potential perspective.

RECOMMENDATION 20: INFORMED CONSENT CONTENT

When patients are considering whether or not to participate in an oncology drug clinical trial, informed consent should include (1) an explanation of clinical research and the rationale for conducting the trial, (2) a complete description of treatment switching (including whether or not it will be available during the study, the conditions under which it may be available, and the rationales for those decisions), and (3) the need for long-term data and follow-up in order to preserve the possibility of adequately adjusting for switching.

When patients participating in an oncology drug clinical trial are deciding whether or not to switch treatments, their treating physician should present them with (1) all treatment options, (2) more specific details about the treatment switching process, and (3) a review of the importance of long-term data and follow-up in order to preserve the possibility of adequately adjusting for switching.

Rationale: Before discussing the details of treatment switching in the specific clinical trial with a prospective study patient, it is critical to provide a contextual framework about clinical research in general and how it intersects with traditional clinical care. The content of this informed consent discussion serves to set patient expectations. One of the most important concepts to convey is that the primary objective of clinical research is to obtain knowledge that may be used to guide treatment
decisions for future patients, and there may or may not be clinical benefit to the study participants.\textsuperscript{62,63} Additionally, in order to be considered ethical, clinical research must have social value and scientific validity, among other attributes.\textsuperscript{5,59} Patients therefore need to be informed about the possible effect of treatment switching on the integrity and value of the trial. They should also be told about how continuing data collection can help mitigate those effects. Such information would be particularly important to patients who enter trials partly or wholly for altruistic reasons – many patients, particularly those with late stage disease, may enter trials to add value and meaning to their lives and need to be aware of factors that could compromise their contributions to developing meaningful science. Finally, from a purely practical viewpoint, providing information about treatment switching up front can also lay the groundwork for patients to cooperate with longitudinal data collection, including at the time of switching and afterwards.\textsuperscript{64,65}

Whether or not treatment switching will be available, under what conditions, and why, are aspects of the study that directly affect patients through the treatments they may receive and obviously should be talked about with patients.

Although, at the time of progression, patients are likely to be more concerned about any additional treatment steps than the details of the study, they cannot make a truly informed decision about whether to switch treatments during the trial without understanding both how the choice could affect them and how it could affect the trial. More detailed information about the process of treatment switching should be provided than before because of the immediacy of the decision. Patients should also be reminded of the limited nature of the information available about the experimental treatment and the importance of longitudinal data collection to statistical adjustments.

\textbf{Implementation:} When an oncology drug clinical trial includes treatment switching, the following information or topics need to be discussed with patients during the informed consent process:

- The primary purpose of clinical research is to gain knowledge and answer an important scientific question. While future patients will benefit from this knowledge generation, patients enrolled in the clinical trial may or may not receive clinical benefit.
- The study is focused on finding which treatment arm works best for most people. Even if the answer to that question were available, it would not mean that that treatment would work the best for them as an individual.
- Information about the benefits and risks of the experimental treatment is limited and incomplete.
- While some new information may become available during the study, the answer to the scientific question will not be known until the study ends and the final analyses are conducted.
- How treatment switching can affect the integrity of the trial results.
- Whether or not treatment switching will be available during the trial.
  - NOTE: treatment switching should not be presented as a guarantee, but as a possible option. Appendix 3 provides some sample language.
- The conditions or times when treatment switching will be allowed (e.g., (a) at the time of personal disease progression, (b) if an interim analysis shows [X results], (c) if external information becomes available during the study that shows [X results].
- Whether or not there will be delays before beginning the new treatment (e.g., if there is a washout period).
- Whether or not treatment switching will be available only during a specified window of time.
An explanation of the data collection points and processes, why they are so critical, and how they relate to treatment switching. Perhaps most importantly, patients should be told that:
  - Data collected at the time of progression and/or the time of switching are particularly vital to enable adjustment for treatment switching.
  - Limited data will still need to be collected for some time after the switch, whether the patient switches to the experimental therapy or to an off-study therapy.

The primary and secondary outcomes and why they were chosen.
  - If a surrogate measure (e.g., PFS) is included as an outcome, what is known about its meaning and how that relates to the length of data collection and the availability of switching.

The study’s definition of “progression,” why it was chosen, and what it means.

If the patient’s cancer progresses, his or her clinician will review all of the possible options, including treatment switching.

Whether or not there will be any additional costs associated with treatment switching (does not have to be in detail at this point).

In the situation that the experimental drug is available outside the study, that it could be harmful if they take it outside the protocol.

If a patient’s disease has progressed and he or she is considering whether or not to switch treatments, new information or topics that need to be discussed (in addition to review of the earlier topics) include:

- All of the patient’s possible treatment options, including treatment switching.
- Whether or not there will be delays before beginning the new treatment and how long they will be.

Appendices 4 and 5 provide the above points in the form of checklists that sponsors and researchers can use to be sure they have included all relevant information concerning treatment switching.

Limitations: Not all of the enumerated topics will necessarily be appropriate for a given trial. Also, as previously discussed, sponsors and researchers should develop robust, comprehensive educational materials for patients and clinicians.
**SECTION V: SUPPLEMENTAL RECOMMENDATIONS**

The discussions accompanying the recommendations in the prior four sections have identified some specific areas where additional research is needed in order to optimally implement the best practices. This section, in contrast, contains more general propositions that do not need to be implemented now as part of the best practices, but that would provide clear benefits if they were to be put into practice in the future.

**RECOMMENDATION 21: PRE-COMPETITIVE COOPERATIVE RESEARCH**

Study sponsors and researchers who share a common interest in a broadly applicable or fundamental scientific issue relating to treatment switching, such as the identification and validation of surrogate outcomes for overall survival, should ideally undertake appropriate research as a joint endeavor.

**Rationale:** Any number of researchers who are active in a particular cancer field would have a shared interest in better defining certain covariables and relationships. Defining the relationship between PFS and OS in patients with metastatic non-small cell lung cancer, for example, would be of value to every researcher in that space. Similarly, identifying prognostic variables for outcomes or for treatment switching would be widely relevant. Because research resources are finite and data can be expensive and difficult to collect, appropriate relevant research questions could be investigated as joint projects among researchers and sponsors in order to avoid redundant and wasteful efforts. Such endeavors potentially could take advantage of different participants’ access to different data sources and also provide quicker results. Ultimately the cooperation would provide benefit to patients.

**Implementation:** There are a number of different models that potentially could be used, including outsourcing the research to a third party that is financed by participating sponsors and researchers, public-private partnerships, and dedicated internal personnel and resources with communication links, among others. The National Cooperative Research and Production Act of 1993 (“NCRPA”) limits the antitrust liability of qualifying and participating joint ventures.66

**Limitations:** Parties may be reluctant to participate because of possible free riders and spillover effects. NCRPA protection may be limited.

**RECOMMENDATION 22: CLINICAL TRIAL RESULTS REPORTING AND DATA SHARING**

In order to help maximize the utility of these best practices, stakeholders should support initiatives to (1) ensure that all clinical trials are publicly registered and results reported, and (2) encourage the sharing of data on the individual patient level provided that appropriate safeguards are in place to protect the interests of patients, researchers, and sponsors. Research funders should make funding contingent on recipients registering the study and providing the results. Before deciding to participate, patients and clinicians should consider whether sponsors and researchers plan to register the study and share its results, which actions would help maximize the value of their participation and contributions.

**Rationale:** One of the problems with searching for data from sources other than the immediate study, particularly from RCTs, is that not all study results are published or otherwise made available and even the existence of studies may not be known.67 In the US, for example, despite legislation requiring all sponsors of phase 2 to 4 drug, biologic, and device trials to register their studies and results in a public database, almost half of cancer drug trials were still not publicly available, either in the database or in the published literature, three years after they had been completed.68 Ideally, shared data from external
clinical trials would be on the patient level. Having access to such data would provide sponsors of studies with high degrees of treatment switching more flexibility in supporting analytical adjustment methods (e.g., allowing subgroup analysis and comparisons with external trial data adjusted for different patient characteristics) and also generate broader societal benefits.\textsuperscript{67,69} While there are valid concerns about data sharing that need to be addressed, e.g., damage to a researcher’s reputation or career as a result of inappropriate analyses or loss of opportunity to conduct secondary analyses,\textsuperscript{70} other arguments against the practice do not appear to be convincing.\textsuperscript{71} Patients, clinicians, and research funders can all take action to accomplish this recommendation and maximize the value of their participation.

**Implementation**: Data sharing already seems to be increasing among academic researchers, health regulatory agencies, and some pharmaceutical companies.\textsuperscript{69,72} For example, a number of life sciences companies have committed, through the website clinicalstudydatarequest.com, to providing researchers with access to patient level data from their clinical trials under certain conditions.\textsuperscript{73} The International Committee of Medical Journal Editors has also proposed requiring authors to share deidentified individual-patient data underlying the results presented in a published article no later than 6 months after publication.\textsuperscript{74}

**Limitations**: There will be costs associated with preparing data for sharing, particularly patient level data. As previously noted, safeguards will need to be taken to protect researchers’ opportunities to conduct secondary analyses and to prevent inappropriate analyses.
APPENDIX 1: REVIEW OF SELECTED STATISTICAL ANALYTICAL METHODS

This appendix reviews characteristics of four methods for evaluating treatment effect on overall survival in the presence of treatment switching, three of which involve statistical adjustments to the study data to account for the observed switching. Although additional methods of adjustment exist, they have not been evaluated sufficiently to recommend at this time, or are quite likely to provide biased or unstable results, or rely upon improbable assumptions. For example, as explained in Recommendation 5, naïve approaches like excluding switchers or censoring them at the time of the switch are not appropriate. Methodologies do evolve, however, and research in this area is ongoing. Sponsors and researchers are well-advised to monitor the appropriate literature to be aware of any relevant developments.

(1) Intention-to-Treat (“ITT”)

ITT analysis compares treatment groups as they were initially randomized, regardless of whether treatment switching occurred. Many regulatory authorities and other stakeholders consider ITT results to be the most trustworthy.

Assumptions
For patients lost to follow-up, there is an assumption those with and without complete follow-up are exchangeable.\(^\text{16}\) Also, ITT analysis assumes that patients’ treatment choices after the trigger event reflect the same choices they would make outside of the clinical trial if they received their assigned treatments initially.

Limitations
If the study drug is beneficial, the ITT analysis tends to be conservative in that it will underestimate the treatment effect of the therapy when treatment switching occurs.\(^\text{13,18,51}\) In fact, the higher the proportion of control group patients who switch, the more questionable an ITT analysis becomes.\(^\text{16}\) In the presence of substantial treatment switching it is not useful for economic evaluations, which generally attempt to compare a state of the world in which the new therapy is used compared to one in which it is not.\(^\text{13}\)

Considerations
Although the ITT analysis is conservative when the treatment is beneficial, it does provide a valid test of the null hypothesis.\(^\text{16}\) It uses data from all randomized patients and maintains the original randomization, which reduces the possibility of bias.\(^\text{51}\)

Recommendations
The ITT approach is widely used for analyzing clinical trial data and should be conducted and reported regardless of the degree of treatment switching because of the limitations associated with the adjustment methods.\(^\text{13,51}\) When crossover is very infrequent, all the methods should yield similar results and it would be appropriate to use the ITT as the primary analysis and the other methods as sensitivity analyses.\(^\text{18}\) Additionally, if the treatment effect in the experimental group is believed to be relatively small (hazard ratio of around 0.75 to 1.00) and/or the treatment effect is likely to be considerably reduced in switchers (by \(\geq 25\%\)), an ITT approach may result in the least biased estimate.\(^\text{13}\) It is otherwise not recommended as the primary analysis for evaluating the causal effect of the study drug on OS in the presence of treatment switching, particularly in the case of high levels of switching.\(^\text{18}\)
(2) Marginal Structural Models ("MSMs") with Inverse Probability of Censoring Weighting ("IPCW")

Marginal structural models ("MSMs") are used to estimate the causal effect of a time-dependent treatment by adjusting for time-dependent confounding. MSMS mimic a randomized trial by assigning dynamic weights to observations of each patient, where the weights take into account the probability of receiving the treatment and the probability of remaining under observation given the information available at each time point.

MSMs include the inverse-probability-of-censoring weight ("IPCW") approach as a special case. In the IPCW approach, and in the context of treatment switching, control group patients who did not switch but who are similar to control group patients who did switch are assigned higher weights in order to reflect the switchers (who are censored at the point of switch). The weight assigned is based on patient characteristics that are causal prognostic factors for mortality and influence the probability of switching.

Assumptions

The MSM with IPCW assumes that there are no unmeasured confounders: that is, data must include all baseline and time-dependent covariates that affect mortality that also predict treatment switching. Another assumption is that the probability of receiving the treatment must be greater than zero in the period that the weighting models are applied to, often referred to as the positivity condition or experimental treatment assumption. The models that characterize treatment switching and censoring risk must be correctly specified, and the Cox model for the treatment effect also must be correctly specified. For identifying the causal effect, the MSM approach also assumes that a patient’s counterfactual outcome under his/her observed treatment history is precisely her observed outcome, also referred to as the consistency condition.

Limitations

The assumption of no unmeasured confounders cannot be tested directly. Sensitivity analyses can be performed, however, to examine the impact of the confounding caused by unmeasured confounders on the causal treatment effect estimates. It is important to note that time-varying covariates may influence switching more than baseline covariates and therefore need to be measured quite close to the time of switching – otherwise it may not be clear whether the covariate value changed before switching and bias could be introduced. An alternative approach might be to use instrumental variables to control for unmeasured confounding.

As noted above, the IPCW method uses the control group patients who did not switch as the basis for adjusting; if there are not a sufficient number of non-switchers, the adjustment will be unstable. Simulations have demonstrated high levels of bias when around 90% of control group patients switched (equivalent to around 20 patients in the control group who did not switch). One rough rule of thumb is that around seven events (or non-events) are needed per covariate to obtain good models.

The positivity condition can be violated when a subgroup corresponding to a particular combination of time-dependent covariates switches treatment. Moreover, model estimation can be very unstable when patients with a very high probability of switching did not in fact switch, because these patients will be assigned extremely large weights and thus result in highly influential observations. Stabilized weights can be used to reduce the variability of the weights. However, when there are very strong covariate-treatment associations, the MSM estimates will still be highly variable. In general, the MSM approach usually requires a relatively large sample size because adjustment is based entirely on observed covariates. The estimation of the weights with small data sets could be problematic. Results of MSM
also can be sensitive to model specifications. Finally, this approach requires continued collection of data on prognostic covariates after the trigger event.

Considerations
Although on theoretical grounds MSMs are an elegant approach, lack of data on the precise time-dependent confounders can jeopardize the calculation of valid weights. Data on key predictors of treatment switching, like patient preference, need to be collected beginning at baseline and continuing past treatment discontinuation or the trigger event. The common treatment effect assumption is not required.

Recommendations
The MSM with IPCW approach can be implemented in standard statistical software such as Stata and SAS. It is recommended for the evaluation of causal treatment effect in trials with a large sample size, where only a moderate proportion of patients cross over and sufficient information regarding potential confounding factors is available.

(3) Rank-Preserving Structural Failure Time Models (“RPSFTMs”)

The RPSFTM estimates “counterfactual survival times” for patients who switched treatments. Counterfactual survival times are the times that would have been observed if the switchers had remained in the control group. An RPSFTM approach maintains the original randomization assignment and provides a randomization-based estimate of treatment effect. The g-estimation method (basically a grid search across an inclusive range of possible values for the treatment effect) is used to determine a value for the treatment effect so that the counterfactual survival time is independent of the randomized treatment group according to a test statistic evaluating independence. Iterative parameter estimations (“IPEs”) are similar to RPSFTMs but use a parametric estimation procedure instead of g-estimation.

Assumptions
The RPSFTM assumes there is a common treatment effect: that the relative treatment effect is the same regardless of when the experimental treatment is initiated, relative to the length of time for which it was taken. In other words, for any given length of study treatment, the drug causes a constant reduction in time to death, assumed equal for all patients before and after progression. A second assumption is that counterfactual survival times are independent of treatment assignment, which is usually a valid assumption if randomization is balanced. An IPE approach makes the additional assumption that the data follow a parametric distribution.

Limitations
Assuming a common treatment effect may be questionable because the disease may be more advanced among switchers and the treatment less effective. Counterfactual censoring times may be informative as they may be associated with prognosis because prognosis may influence if and when a patient switches treatment. To break this relationship, recensoring is required, which involves artificially censoring the observations of some patients at an earlier time-point. Although this approach avoids informative censoring bias, it may lead to other biases if the treatment effect changes over time.

If the control group uses an active treatment, several additional assumptions about treatment strategies and their effectiveness must be made because the model requires that patients be either “on treatment” or “off treatment” and the “off treatment” category would include two different types of treatments.
The RPSFTM also assumes that the treatment effect occurs only while “on treatment” and does not persist after the therapy is discontinued. If a continuing treatment effect is expected, it is necessary to either assume a lagged treatment effect or consider patients who take the experimental therapy to always be “on treatment” from that time until their deaths (known as analyzing on a “treatment group” basis). Sensitivity analyses that manipulate assumptions to examine their impacts on the outcomes (e.g., reducing post-progression efficacy by [X]%) may provide insights to the analyses.

Considerations
The common treatment effect assumption is unlikely to be absolutely true; the main issue is whether it is likely to be approximately true – simulations have demonstrated that the method performs well when the assumption holds. The RPSFTM does not require the assumption of no unmeasured confounders. Additionally, modeling the covariate effects is possible but not required, and RPSFTM can be implemented in standard statistical software such as Stata and SAS. This method maintains the significance levels associated with the ITT analysis, but loses power due to treatment switching so confidence intervals may be relatively wide.

Recommendations
The RPSFTM would be preferable to the MSM/IPCW for smaller trials with relatively little information on covariates, and is also suitable for trials in which a large proportion of patients switch as well as in larger trials, depending upon the validity of the common treatment effect assumption.

(4) Two-Stage Methods

Two-stage methods model the effect of switching on the residual lifetime after the secondary baseline (e.g., disease progression) among control group patients. In the analysis, the time of the trigger event is treated as the (secondary) baseline and a parametric accelerated failure time model that incorporates covariates measured at the time of progression is used to fit the post-progression survival. The counterfactual survival time in the absence of treatment switching is then estimated for all switchers using the treatment effect estimated by the fitted model. The treatment effect, adjusted for treatment switching, on overall survival can then be estimated.

Assumptions
The “no unmeasured confounders” assumption must hold at the time of the secondary baseline. The post-progression survival in the control arm is assumed to follow a parametric accelerated failure time model.

Limitations
This approach requires treatment switching to occur soon after the trigger event as there is no attempt to adjust for time-dependent confounding beyond the trigger event. Data collected must include all baseline and time-dependent covariates that affect mortality.

Considerations
A key consideration for a two-stage approach is that the parametric survival model be appropriate to the data. Assessing the goodness of fit of the accelerated failure time model used is also very important for this to be a valid approach. Unlike the RPSFTM, a two-stage approach does not have to assume that the treatment effect in switchers is the same as the treatment effect in experimental group patients, and does not require data to be collected on confounders beyond the trigger event. Confidence intervals
are likely to be wide when the data are relatively sparse, although two-stage methods appear to be less sensitive to this situation than the MSM/IPCW.

**Recommendations**

This approach can be useful when patients switch treatment after the trigger event. The approach is likely to work best when the switching proportion is neither too high nor too small, in order that the survival times in switchers and non-switchers can be robustly compared. In addition, data on potential confounding factors associated with disease prognosis and treatment switching must be collected at the time of the trigger event and switching must occur soon after the trigger event.
APPENDIX 2: EVALUATING THE QUALITY OF EXTERNAL EVIDENCE AND DATA SOURCES

RECOMMENDATION APPX-1: QUALITY OF EXTERNAL EVIDENCE AND DATA SOURCES

Clinical study sponsors and researchers should systematically assess the quality of any external data and data sources they are considering using to support their chosen analytical adjustment method, preferably by using published quality checklists or scales. This recommendation applies to all external evidence, whether from a randomized controlled trial or observational data sources. The term “quality,” in this context, refers not only to features like data completeness and accuracy, but also extends to the confidence that the design and conduct of the data source are protected from bias.78

Rationale: Data external to a clinical trial may come from other randomized controlled trials (“RCTs”) or from observational sources. Data from RCTs are generally considered to be high quality data because of the rigorous process involved with their collection. Under Good Clinical Practices as set forth by the International Conference on Harmonisation, study sponsors must, among other things, implement and maintain quality assurance and quality control systems, ensure that all data are reliable and have been processed correctly, and appoint monitors to verify that the reported trial data are accurate, complete, and verifiable from source documents.79 Nevertheless, flaws in design (particularly inadequate allocation concealment or blinding), conduct, or analysis can lead to bias,80,81 and sponsors and researchers should not accept external RCT data uncritically.

Potential sources of observational data include administrative/claims databases, electronic health records (“EHRs”), and registries, among others.35 Some of these databases are quite large, making it more difficult to achieve the same sort of data quality as in clinical trials.82 Routine medical care data, such as those in EHRs, do not typically undergo the quality system checks of RCTs83 and can reflect recording biases and data quality issues (e.g., invalid, inconsistent, or missing data).34 Neither EHRs nor administrative databases are designed with research objectives in mind and the reliability of any particular data field element can vary with its importance to the purpose of the database.36,82 In administrative databases, for example, reimbursed procedures are more likely to be accurately coded than comorbidities, for which ICD-9 codes may be only 15-20% sensitive.36,84 Such issues are not without consequence: applying the same study design to different databases can yield substantially differing results.37

Implementation: With respect to RCTs, a number of different instruments, including scales and checklists, exist for assessing their quality. (Both scales and checklists utilize items that measure quality but scales summarize the evaluation by providing a single final score.85) One systematic review of published scales used to evaluate the quality of RCTs found that the majority had not been developed following methodological standards and had not been tested for validity and reliability in the areas to they were being applied.85 The Jadad Scale,86 however, was widely used, presented the best validity evidence, and had been tested for reliability in different settings.85

As regards RCT checklists, the Consolidated Standards of Reporting Trials (“CONSORT”) 2010 checklist87 is one of the most widely used and endorsed.88,89 Although CONSORT 2010 does not explicitly recommend how to design, conduct, or analyze RCTs, the prospect of deficiencies being identified through the reporting process provides indirect incentive to researchers to maintain or improve trial quality.87 Alternatively, the Cochrane Collaboration in 2011 published a revised risk of bias tool (“CCRBT”) for assessing randomized trials81,90 that is often used, particularly for systematic reviews in a
wide variety of areas (e.g., urology,\textsuperscript{91} enhanced recovery pathways in lung resection,\textsuperscript{92} and pharmaceutical treatment of alcohol dependence\textsuperscript{93}). The CCRBT has been reported as having only slight to fair inter-rater reliability, however, perhaps related to its level of subjectivity, and as needing more thorough validation of its psychometric properties.\textsuperscript{94} At the present time in this evolving area, using the CONSORT 2010 list as a guide to identify aspects of an RCT that could potentially result in biases may be the most useful check on study quality although other approaches may be used as well.

For assessing the value of data from observational databases, researchers should determine what quality assurance checks have been performed. While data cleaning has value in confirming the quality of some aspects of observational datasets, frequent source-to-database data audits may be a critical step\textsuperscript{83} and should be assessed. Other key checks to look for include examination of missing and out-of-range values, data consistency, and seeking of duplicates, among others.\textsuperscript{23} Researchers should also review the published literature for any descriptions of the database’s reliability and validity and, if appropriate, compare data figures to established norms.\textsuperscript{23}

To fully evaluate observational databases, however, it is necessary to examine not just the quality of the evidence, but also the quality of the design and implementation of the database or registry.\textsuperscript{78} FDA, in developing criteria for assessing the quality of genetic databases, has proposed examining three classes of factors: (1) data quality (e.g., source of evidence is recorded, full recording of database versions and tools, analytical tools are validated); (2) database operations quality (e.g., SOPs reviewed on annual basis, adequate security measures and patient privacy protections, plan for long-term sustainability); and (3) curation and personnel (e.g., curation performed by full-time qualified experts who receive adequate training and have their proficiency tested regularly).\textsuperscript{95,96} Alternatively, the Data Quality Collaborative has suggested using the following four domains to organize review: data definition, data acquisition, data processing, and data element characterization.\textsuperscript{34}

The Agency for Healthcare Research and Quality (“AHRQ”), in its publication, “Registries for Evaluating Patient Outcomes: A User’s Guide,” provides a detailed series of tables listing indicators of registry quality both for establishing and operating registries and for assessing data quality.\textsuperscript{78} Cochrane Methods also has developed a tool for assessing the risk of bias in non-randomized studies.\textsuperscript{28} These lists are useful both to (1) researchers in evaluating external data sources and reporting to decision makers, and (2) decision makers in reviewing submitted analyses.

**Limitations:** As noted above, many of the published methods of evaluating the quality of RCTs were not developed following methodological standards and are being used for purposes for which their validity and reliability have not been tested.\textsuperscript{85} Research on the quality aspects of registries remains “relatively sparse,”\textsuperscript{78} and existing guidelines to assess the quality of observational studies, including data quality, contain substantial variations and contradictions.\textsuperscript{97} Until a comprehensive data quality assessment framework is developed, appropriately evaluated, and supported by broad consensus, specific guidance on the implementation of this recommendation must remain relatively broad and include a range of possible approaches.
APPENDIX 3: SAMPLE INFORMED CONSENT LANGUAGE
Provided below is some sample language that illustrates presenting treatment switching as a possible option, not as a guarantee:

“If [describe criteria – e.g., your disease progresses as determined by your doctor based on imaging studies and your clinical condition], you may have the opportunity to switch over to the other treatment arm. You and your doctor will make that decision together based on the available information -- it may or may not make sense for you at the time. We will still not know what the answer to the study question is and the other treatment may or may not give you good results.”
APPENDIX 4: INFORMED CONSENT AT STUDY ENTRY: TREATMENT SWITCHING CHECKLIST

The primary purpose of clinical research is to gain knowledge and answer an important scientific question. While future patients will benefit from this knowledge generation, patients enrolled in the clinical trial may or may not receive clinical benefit.

The study is focused on finding which treatment arm works best for most people. Even if the answer to that question were available, it would not mean that that treatment would work the best for them as an individual.

Information about the benefits and risks of the experimental treatment is limited and incomplete.

While some new information may become available during the study, the answer to the scientific question will not be known until the study ends and the final analyses are conducted.

How treatment switching can affect the integrity of the trial results.

Whether or not treatment switching will be available during the trial.

NOTE: treatment switching should not be presented as a guarantee, but as a possible option.

The conditions or times when treatment switching will be allowed (e.g., (a) at the time of personal disease progression, (b) if an interim analysis shows [X results] results, (c) if external information becomes available during the study that shows [X results].

Whether or not there will be delays before beginning the new treatment (e.g., if there is a wash-out period).

Whether or not treatment switching will be available only during a specified window of time.

An explanation of the data collection points and processes, why they are so critical, and how they relate to treatment switching. Perhaps most importantly, patients should be told that:

Data collected at the time of progression and/or the time of switching are particularly vital to enable adjustment for treatment switching.

Limited data will still need to be collected for some time after the switch, whether the patient switches to the experimental therapy or to an off-study therapy.
The primary and secondary outcomes and why they were chosen.

If a surrogate measure (e.g., PFS) is included as an outcome, what is known about its meaning and how that relates to the length of data collection and the availability of switching.

The study’s definition of “progression,” why it was chosen, and what it means.

If the patient’s cancer progresses, their clinician will review with them all of their possible options, including treatment switching.

Whether or not there will be any additional costs associated with treatment switching (does not have to be in detail at this point).

It could be harmful if they take the experimental drug outside the protocol. (NOTE: include only if the experimental drug is already available on the market.)
APPENDIX 5: INFORMED CONSENT AT TIME OF PROGRESSION: TREATMENT SWITCHING CHECKLIST

_______ All of the patient’s possible treatment options, including treatment switching.

_______ The study is focused on finding which treatment arm works best for most people. Even if the answer to that question were available, it would not mean that that treatment would work the best for them as an individual.

_______ Information about the benefits and risks of the experimental treatment is limited and incomplete.

_______ While some new information may have become available during the study, the answer to the scientific question will not be known until the study ends and the final analyses are conducted.

_______ How treatment switching can affect the integrity of the trial results.

_______ Whether or not there will be delays before beginning the new treatment (e.g., if there is a wash-out period).

_______ Whether or not treatment switching is available only during a specified window of time.

_______ Review the importance of data collection points:

_______ Data collected at the time of progression and/or the time of switching are particularly vital to enable adjustment for treatment switching.

_______ Limited data will still need to be collected for some time after the switch, whether the patient switches to the experimental therapy or to an off-study therapy.

_______ The primary and secondary outcomes and why they were chosen.

_______ If a surrogate measure (e.g., PFS) is included as an outcome, what is known about its meaning and how that relates to the length of data collection and the availability of switching.

_______ The study’s definition of “progression” and what it means.

_______ Whether or not there will be any additional costs associated with treatment switching (in detail if there are additional costs)

_______ It could be harmful if they take the experimental drug outside the protocol. (NOTE: include only if the experimental drug is already available on the market.)
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