PROGRAM DESCRIPTION

OFFICE OF MEDICAL POLICY

Safety Outcomes Trials Subcommittee

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PURPOSE

This document describes the organization, membership, responsibilities, and procedures of the Safety Outcomes Trials Subcommittee of the Medical Policy Council (MPC) in the Center for Drug Evaluation and Research (CDER).

BACKGROUND

A safety outcomes trial (SOT) is a prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome (single or composite) such as irreversible morbidity or mortality as the primary trial endpoint. SOTs are typically large trials designed to assess whether a treatment increases the rate of certain clinical adverse events known to occur commonly in a treatment population (e.g., heart attacks, strokes) and that would therefore not be readily interpretable as drug related in the absence of a control group. This is in contrast to assessment of relatively rare events, such as agranulocytosis or Stevens-Johnson syndrome, which would be interpretable as single events in the absence of a control group.

SOTs have been required prior to approval when a drug was considered a potential cause of a serious adverse outcome on the basis of a preliminary signal or because of a concern about an entire class of drugs, as was the case for inotropic agents used in the treatment of heart failure and for anti-arrhythmic drugs, two classes of drugs in which outcome trials intended to show effectiveness instead showed increased serious adverse event; (e.g., CAST for anti-arrhythmia; PROMISE for heart failure). SOTs have been issued as post-marketing requirements (PMRs) under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, after some degree of reassurance about the safety concern from the pre-approval data.

In diabetes drug development, for example, SOTs have been used to rule out excess risk of major adverse cardiovascular events (MACE). In these cases a reason for seeking such trials is the expected very long duration of use, the vulnerability of the population, the largely "preventive" effect (as opposed to early benefit) of the drugs together with early suspicion that some antidiabetics caused increased cardiovascular risk. Although most SOTs have assessed cardiovascular events as the primary endpoints (particularly for NSAIDs and drugs for heart failure, arrhythmia, diabetes, and obesity), large outcomes trials have also assessed the rates of serious asthma exacerbations, cancer and other important safety endpoints. Although not commonly used in other settings, SOTs could be used to assess clinical safety endpoints such as infection, lymphoma, suicidality, and fractures. These types of adverse outcomes are known to occur in the general population, and, therefore, controlled observations in an outcomes trial may be necessary to determine whether exposure to certain drugs increases the rates of these events.

SOTs can potentially provide critical evidence about both short- and long-term risk. In general, the populations studied should be ones that have a relatively high risk of the event or events of interest (e.g., for cardiovascular events, the trial population would need to include older patients and have cardiovascular risk factors) and be likely to adhere to the treatment. SOTs are generally large, expensive, long-term studies. It is therefore critical that their potential feasibility and overall utility be carefully assessed.

As a subcommittee of the CDER Medical Policy Council, the Safety Outcomes Trials Subcommittee will serve as an advisory body on safety outcomes trials being considered within CDER. In general, all safety outcomes trials under active consideration by review divisions should be evaluated by the Subcommittee. The Subcommittee would not review SOTs that are part of established guidance, such as those for diabetes drugs, unless changes in practice are being considered.

The Safety Outcomes Trials Subcommittee will serve the following primary functions:

- Provide advice to OND review divisions when SOTs are being considered as pre- or post-approval requirements. The goals are to help assure that SOTs are well-designed, feasible and needed (e.g. that the safety concern is plausible and cannot be resolved using an observational study) to encourage a consistent and sound policy across the Center
- Catalog and analyze the ongoing experience with SOTs to inform future decision-making
- Assist in the development of guidance documents that articulate principles and best practices for the development and conduct of SOTs

For each SOT reviewed, the Subcommittee will assess the rationale for the proposed safety outcomes trial. The Subcommittee will also assess whether the proposed SOT is optimally designed to detect the safety concern of interest. This would include

considerations such as the trial population, control group, endpoints, duration and probable persistence of treatment, statistical methods, and sample size.

For pre or post-approval SOT requirements being considered, the Subcommittee's review would take place as soon as feasible once a SOT requirement is being considered. In addition, if a specific protocol has been developed and there are remaining issues based on the earlier discussions it should be presented for review.

RESPONSIBILITIES

Responsibilities of the Subcommittee Members:

- Provide advice on the appropriateness and design of safety outcomes trials recommended by CDER divisions. This advice will in many cases precede development of a final protocol.
- Serve as a forum for scientific evaluation and discussions involving safety outcomes trials ensuring consistency and sound policy across divisions and CDER.
- Inventory and review safety outcomes trials that have been recommended or required and carried out to learn from previous experience and inform policy.

Responsibilities of the Subcommittee Chair:

- Provide leadership and direction to the Subcommittee.
- Work with review division to identify and prioritize issues for consideration by the Subcommittee.
- Promote involvement and balanced participation of all members.
- Consult with the Medical Policy Council on any issues/positions where the Subcommittee would benefit from a senior level discussion.
- Provide annual updates on Subcommittee decisions and actions to the Medical Policy Council.

Responsibilities of the Executive Secretary:

- Confirm meeting agendas and conduct meetings.
- Apprise the Subcommittee Chair of progress and activities.
- Ensure that the Subcommittee repository in the Medical Policy Council's electronic database includes meeting minutes, log and status of issues discussed and assignments made, copies of the Subcommittee decisions and actions, and any other related documentation.
- Catalog and characterize all pre- and post-approval safety outcomes trials required by FDA.

Responsibilities of the CDER review division/office seeking Subcommittee evaluation:

- When the review division is considering an SOT or has received a protocol requiring further discussion, contact the Executive Secretary for consideration by the Subcommittee Chair with a timeline of when the discussion needs to take place to meet PDUFA goals or other regulatory considerations.
- Provide a 3-5 page brief to the Executive Secretary no later than 2 weeks before the Subcommittee meeting. The brief should provide all the necessary information to understand the review division/office's intended recommendation to require a safety outcomes trial for a development program, including the reasons for recommending the trial, choice of study endpoints, patient population, and justification of the risk margin to be ruled out by the study. The brief may also include questions for the Subcommittee to consider.
- Identify a lead from the review division/office seeking Subcommittee evaluation.
- Submit a list of meeting attendees to the Executive Secretary.

PROCEDURES

Subcommittee activities regarding safety outcomes trials:

1. The meetings will be held at the request of a review division/office considering an SOT for a development program. It will seek a meeting as early as feasible during its consideration and should not generally wait for a final protocol. The review division/office will submit a briefing document to the Subcommittee Chair and Executive Secretary for consideration.
2. The Subcommittee Chair will consider the review division recommendations for safety outcomes trials and prioritize them for consideration with appropriate input from Subcommittee members.
3. A Subcommittee meeting will be convened.
    - Experts from CDER and Agency staff will be identified and invited at the Subcommittee Chair's discretion to participate in the discussion.
    - The individual and/or office seeking Subcommittee evaluation will provide an overview of the recommended safety outcomes trial at the beginning of the meeting.
    - Final recommendations will be established through deliberation among, and, as necessary, voting by all Subcommittee members attending the meeting.
        - Much of the purpose of the subcommittee will be served by the active discussion of the subcommittee members and other participants. Where a vote is needed to reach a conclusion, a final vote will be determined by simple majority. The Subcommittee chair will cast a vote in the case of a tie.
    - If the Subcommittee cannot reach a conclusion without further information, the Subcommittee may identify specific questions/concerns for the review division/office to research and provide answers. In such

cases, a second Subcommittee meeting may be held to review the responses. The Subcommittee may also consult with the Medical Policy Council if there are important areas of disagreement among Subcommittee members.

4. Recommendations from the Subcommittee are considered advisory; therefore, if the review division disagrees with the recommendation reached by the Subcommittee, the review division can:
    - Reach a different conclusion, generally with ODE office level input and consideration.
    - Proceed through the Office of New Drug process to discuss opposing points of views regarding a regulatory decision. This may include a Center Director Briefing, procedures outlined in CDER MAPP 4151.8 (Equal Voice), CDER MAPP 4151.1 (Scientific/Regulatory Dispute Resolution) or MAPP 4151.2 Rev. 1 (Resolution of Differing Professional Opinions.
    - Request review by the Medical Policy Council.
        - Requests for consideration by the Council must be accompanied by an explanation of the basis for disagreement with the Subcommittee's recommendation, e.g., public health need, why the study is feasible.
        - The Council, at the discretion of the Medical Policy Council Chair, may respond to the request using one of the following two options:
            - The Chair, with appropriate input from Council members and experts from CDER, may respond to the request in writing.
            - The agenda item may be introduced to the Council at a future meeting.
    - Documentation (such as the request for reconsideration and the response) will be archived with the initial Subcommittee recommendation reached.

Subcommittee activities regarding development of guidance on safety outcomes trials:

1. The Subcommittee will assist in the review of draft guidance documents on the Center's current view regarding the need for, and planning of, safety outcomes trials.
2. Experts from CDER and Agency staff will be sought and invited at the Chair's discretion to participate in the development of the guidance.
3. Safety outcomes trials that have been recommended will be identified and reviewed to inform policy.
4. The draft guidance should be submitted for Medical Policy Council review.

ORGANIZATION

Membership

The MPC Clinical Safety Subcommittee includes the following.

- Chair: Deputy Director for Clinical Science

- Executive Secretary

- Members: Members of this Subcommittee will include 8 representatives from the Office of New Drugs, 2 representatives from the Office of Medical Policy, and 1 representative each from the Office of Surveillance and Epidemiology and the Office of Biostatistics.

- Other participants: A team from the respective review division will participate in the discussion and provide the necessary supporting documents. Observers and consultants from other Divisions, Offices, or Centers will usually be invited, at the discretion of the Subcommittee Chair. The meeting participants other than subcommittee members will be non-voting.

REFERENCES

- CDER MAPP 4301.1, Center for Drug Evaluation and Research Medical Policy Council

EFFECTIVE DATE

This MAPP is effective upon date of publication.