Guidance
Submission of Investigator's Brochure to the Institutional Review Board

Notes
Research protocols developed by industry often involve development and testing of Investigational New Drugs (INDs). The proposal developed by an industry sponsor to test an Investigational New Drug (IND) will include a protocol and an Investigator's Brochure ("IB").

The Institutional Review Board (IRB) does not approve IBs.

What is an Investigator's Brochure ("IB")?
The IB is a compilation of the clinical and non-clinical data on the investigational products that are relevant to the study of the products in human subjects. Its purpose is to provide investigators and others involved in the trial with the information to facilitate their understanding of the rationale for and their compliance with many key features of the protocol like dose, dose frequency, methods of administration, safety monitoring, known risks etc. The same IB can apply to different studies using the same investigational product.

Why does the IRB need to see the IB?
For studies conducted under an investigational new drug application, an IB is usually required by the U.S. Food and Drug Administration (FDA). Even though 21 CFR part 56 does not mention the IB by name, much of the information contained in such brochures is clearly required to be reviewed by the IRB. The regulations outline the criteria for IRB approval of research, requiring risks to subjects being minimized and assuring that the risks to subjects are reasonable in relation to the anticipated benefits. The risks cannot be adequately evaluated without review of the results of previous animal and human studies, which are summarized in the IB.

There is no specific regulatory requirement that the IB be submitted to the IRB. However, there are regulatory requirements for the submission of information which normally is included in the IB. Therefore, it is common, and expected by the Children's Wisconsin IRB, that the IB is submitted to the IRB. This serves as information to the committees in assessing the research and whether the regulatory criteria for approval criteria are met for both new research proposals and modifications to a study.

When should an investigator submit the IB to the IRB?
As mentioned previously, the IRB does not approve IBs; they provide information needed to assess research.

When one exists, the IB should be included in the initial submission for the new project.

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Over the course of the study, the content of the IB may change, and the sponsor will issue a new brochure to investigators.

Updated IBs should be submitted as a separate Reportable Event/New Information package. The package should include the Reportable Event/New Information Form with the submission, and will be acknowledged rather than approved. There may be consultation with Children's Pharmacy, IRB Chair, and/or clinicians depending on the nature of the updates.

When the investigator receives a new IB, the Principal Investigator (PI) should assess the changes and communicate with the sponsor as needed about whether the changes involve risks that warrant action, such as changes to protocol (i.e., eligibility criteria, safety monitoring) or Informed Consent Forms (ICFs)/consent addendums (providing new information to current or prospective subjects). If the sponsor is amending any of the documents, this may be considered a risk mitigation plan and should be described in the Reportable Event/New Information Form.

- Depending on what is included in the update and whether risks are identified, the information could meet the definition of an Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO). The risks could be new, or they could be previously identified risks that have been found to be occurring at greater severity and/or frequency than previously identified. In accordance with Children's Wisconsin IRB policy, these IBs would require prompt reporting (within 5 days of receipt) to the IRB.

    - Even if an amendment is planned to be issued by the sponsor, the IB should still be submitted promptly (within 5 days of receipt), noting that an amendment is pending, because the IRB needs to review the information to determine whether specific immediate action is warranted to protect the rights, safety, and welfare of any subjects who are or who could be enrolled before the amendment is approved.

Possible actions that could be taken by the IRB, should the IB reveal safety concerns, include:

- Temporary or permanent closure of the study to enrollment
- Require revision of informed consent documents
- Require notification of past and/or current subjects
- Require additional safety monitoring

When review of the IB reveals that all changes are administrative, or there are no concerns identified regarding the risk-benefit ratio, these should still be submitted in "real time" (after received but before Continuing Review).