

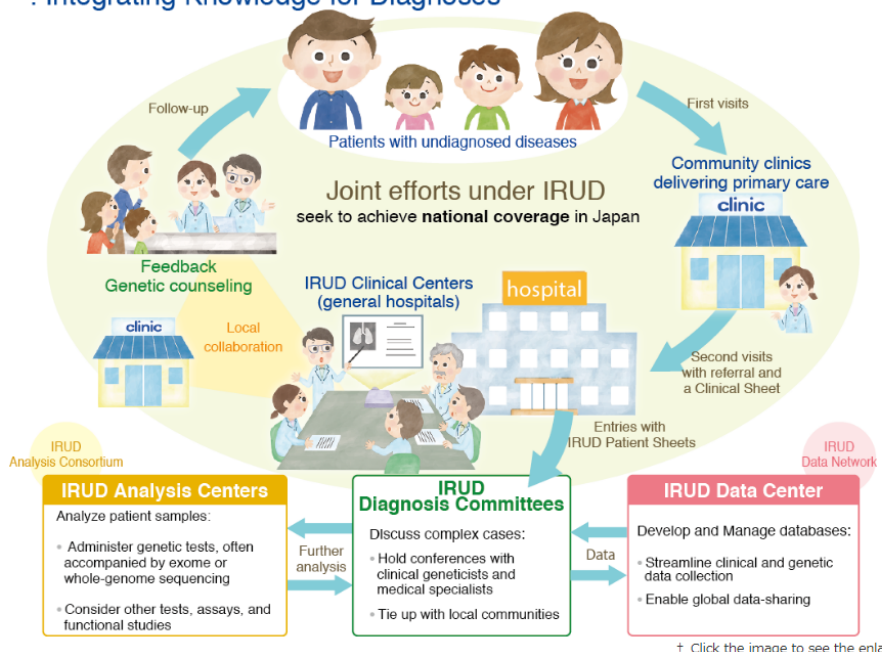
## Orphan Drug Development Guidebook

### Building Block J313

This document defines the content of the Building Block created for each identified tool, incentives, initiative or practice introduced by public bodies or used by developers to expedite drug development in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Japan Agency for Medical Research and Development (AMED) – Initiative on Rare and Undiagnosed Diseases
References	<a href="https://www.amed.go.jp/en/program/IRUD/">https://www.amed.go.jp/en/program/IRUD/</a> <a href="https://www.nature.com/articles/ejhg2017106.pdf">https://www.nature.com/articles/ejhg2017106.pdf</a>
Description	<p>Japan Agency for Medical Research and Development (AMED) leads the Initiative on Rare and Undiagnosed Diseases (IRUD) program. The program provides patients across Japan suffering from undiagnosed diseases with a diagnostic strategy that involves genetic analysis. It also promotes international collaboration through proactive data sharing to enhance research and diagnosis of patients with rare and undiagnosed diseases. The program is constructed of a network of more than 400 local hospitals including 34 IRUD Clinical Centers, where complex cases can be reviews by multi-disciplinary IRUD Diagnosis Committees made up of medical specialists and clinical geneticists working for both adult and pediatric patients.</p> <p>The initiative has now expanded from a diagnostic and data sharing model to a phase named IRUD Beyond, to further advance its research activities:</p> <p>Beyond diagnosis: Translational research of treatment</p> <p>Beyond genotyping: Progressive improvement on the success rate of diagnosis</p> <p>Beyond borders: International collaboration via data-sharing and beyond</p> <p>The procedure of IRUD is as follows:</p>

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	<ol style="list-style-type: none"> <li>1. Patients will be referred to an IRUD Clinical Center from their treating physicians</li> <li>2. Patients will visit IRUD Clinical Centers and IRUD enter the IRUD system</li> <li>3. IRUD Diagnosis Committee will discuss the cases prior to analysis</li> <li>4. IRUD Analysis Centers will perform the analysis and its annotation</li> <li>5. IRUD Diagnosis Committee will make the diagnosis and feedback the result to the community for further follow-up</li> </ol>
Category	Development Practices Building Blocks
Geographical scope	Japan
Availability	Applicants developing medicines for rare and undiagnosed diseases.
Scope of use	<p>The program aims to provide and establish the following systems for patients with rare and undiagnosed disease:</p> <ul style="list-style-type: none"> <li>• A medical system that will enhance the diagnosis in a systematic manner</li> <li>• Accumulation of relevant patient information that will be openly shared among researchers/physicians/public to gather patients with similar phenotypes and promote their diagnosis</li> </ul>
Stakeholders	<ul style="list-style-type: none"> <li>• Patients</li> <li>• Physicians</li> <li>• Researchers</li> <li>• Funding Agencies (eg. AMED) and other regulatory agencies including the Ministry of Welfare Labor and Health (MHLW)</li> </ul>

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	<p><b>Initiative on Rare and Undiagnosed Diseases (IRUD) : Integrating Knowledge for Diagnoses</b></p>  <p>Joint efforts under IRUD seek to achieve national coverage in Japan</p> <p>IRUD Analysis Centers Analyze patient samples: • Administer genetic tests, often accompanied by exome or whole-genome sequencing • Consider other tests, assays, and functional studies</p> <p>IRUD Diagnosis Committees Discuss complex cases: • Hold conferences with clinical geneticists and medical specialists • Tie up with local communities</p> <p>IRUD Data Center Develop and Manage databases: • Streamline clinical and genetic data collection • Enable global data-sharing</p> <p>† Click the image to see the enlarged image.</p>
Enablers/ Requirements	<p>Patients for meet either of the following two criteria that persists for over six months (except for infants), that have not been previously diagnosed, and have symptoms that disable them to pursue activities of daily living.</p> <ol style="list-style-type: none"> <li>1. The patient presents with abnormal physical findings that involve two or more organs and cannot be explained by a single known cause.</li> <li>2. The symptoms suggest a genetical cause, including patients with similar symptoms within the family.</li> </ol> <p>Treating physicians can refer patients who meet the above criteria to one of the IRUD centers for diagnosis. Physicians at IRUD Clinical Centers will see the patient and if a diagnosis cannot be made, the patients genetic analysis will be performed with the patient or their families consent. Relevant clinical and genetic information will be stored at the IRUD Data Center for further research purpose.</p>
Output	<p>Through the IRUD program, patients with undiagnosed, rare disease all over Japan can access an appropriate medical institute that will lead to diagnosis of these patients. This will eventually decrease the number of patients with undiagnosed disease, and improve the diagnostic capability of physicians and other medical personnel at IRUD Clinical Centers.</p> <p>The relevant patient clinical and genetic information will form a database in an internationally accepted format. This will allow the information to be shared not</p>

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	<p>only within IRUD but both domestic and international investigators to potentially identify cases with same genetic abnormality and correlate them with the symptoms to solve the so called “n of 1” problem.</p> <p>The initiative will also enable collaboration with relevant researchers to identify the function of newly found genetic mutations, that will lead to identification of novel diagnostic or therapeutic approaches. Eventually, we expect the findings to expand possibility for finding novel treatment for common diseases. The diagnostic model of IRUD will also be a model for other types of diseases that are difficult to diagnose.</p> <p>The findings achieved through IRUD will not only be distributed in scientific papers and meetings, but also be available to the general public, so that it would increase awareness to rare and undiagnosed diseases. The expectation is to enhance collaboration between medical personnel and patients and their families to a new diagnosis and understanding of currently undiagnosed diseases.</p>
Best time to apply and time window	At the start of drug development
Expert tips:	<p>PROs: The initiative will also enable collaboration with relevant researchers to identify the function of newly found genetic mutations, that will lead to identification of novel diagnostic or therapeutic approaches</p> <p>CONs: Patients have to meet the above criteria to be enrolled in the system (for instance, the outreach cannot be expanded to patients with a single organ disease).</p>