Drug and Biologic Preclinical and Clinical Trial Definitions

Phase	Population	- Number of Subjects Required*	Purpose
Pre-clinical	Highly controlled (GLP) studies in animals	Hundreds to Thousands	Safety, toxicity, effectiveness. Provides evidence to FDA safe enough to try in humans
0	Healthy volunteers Exception: Cancer/AIDS etc.	10 to 15 subjects/trial	Limited exposure, short duration, with no therapeutic or diagnostic Intent. Helps identify promising candidates and assess feasibility for further development. Particularly useful when developing products for serious diseases. Often referred to as Exploratory IND studies.
1	Healthy volunteers Exception: Cancer/AIDS etc.	20 to 80 subjects/trial	Safety
2	Subjects with the Illness (narrow population)	24 to 300 subjects/trial	Safety Effectiveness Dose
3	Subjects with the Illness (broad population)	250 to 3000 subjects/trial	Confirming safety and effectiveness in diverse populations
4	Subjects with the Illness; Special population (very broad population)	FDA and Sponsor negotiate	After FDA approval (Post-licensure), for safety and/or other uses

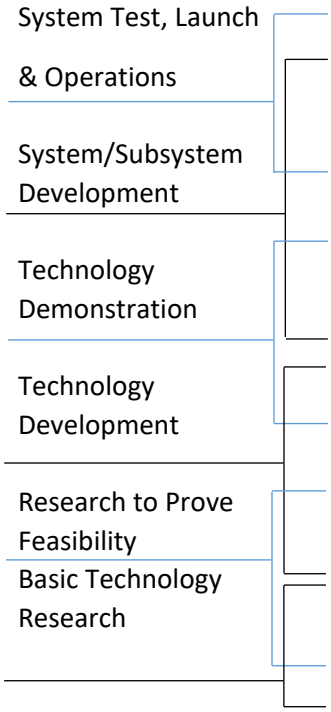
*The number of subjects in a clinical trial varies greatly by the type of product and FDA input/feedback

Biomedical Technology Readiness Levels

D – Pharmaceutical (Drugs); B/V- Pharmaceutical (biologics, Vaccines); Same for All

Biomedical Technology Readiness Levels

MD – Medical Devices



TRL 9 Post marketing studies/surveillance. Post-marketing studies may be required.

TRL 8 CDRH approval of Premarket Approval (PMA), or as applicable, 510(k)

TRL 7 Class III clinical end points and test plans are agreed upon by CDRH. For 510(k), final prototype and/or initial commercial-scale device is produced and tested in a military operational environment; info and data support preparation of 510(k).

TRL 6 Class III device safety demonstrated, support proceeding to clinical safety and effectiveness trials. For 510(k), info and data support production of final prototype and final testing in a military operational environment.

TRL 5 Investigational Device Exemption (IDE) review by CDRH results in determination that investigation may begin. For 510(k), prelim findings suggest the device will be substantially equivalent to a predicate device.

TRL 4 PoC and safety of candidate devices/systems are demonstrated in defined laboratory / animal model(s).

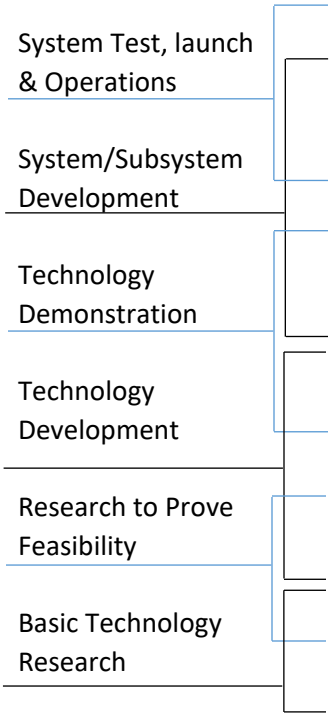
TRL 3 Hypothesis testing and initial proof-of-concept (PoC) demonstrated in limited number of laboratory models.

TRL 2 Hypothesis(es) generated. Research ideas and protocols developed.

TRL 1 Maintain scientific awareness; tech watch. Scientific literature reviews and market surveys initiated and assessed.

Biomedical Technology Readiness Levels

Medical IM/IT & Medical Informatics



TRL 9 Product successfully used in military mission as part of Initial Operational Test and Evaluation (IOT&E). Logistical Demonstration successfully conducted.

TRL 8 Development Test & Evaluation (DT&E) of the HW/SW system in its intended environment. Demonstrated it meets design specifications. Validated in several operational environments.

TRL 7 System is operationally integrated and tested with target applications in operational environment with end users.

TRL 6 System tested with interfaces & support systems in relevant or simulated operational environment. Configuration Management Approach Developed.

TRL 5 Models are implemented into data/knowledge system & tested in lab environment. Actual interfaces specified.

TRL 4 Prototype produced. HW/SW pieces work together. Models use real data/knowledge.

TRL 3 Data and knowledge representation schema modeled.

TRL 2 System concepts documented. Schema defined. Data and knowledge representation issues defined.

TRL 1 Identified potential medical solution to mission need. Defined data & knowledge representation Issues.

Step 1: Determine the Knowledge Product (KP):

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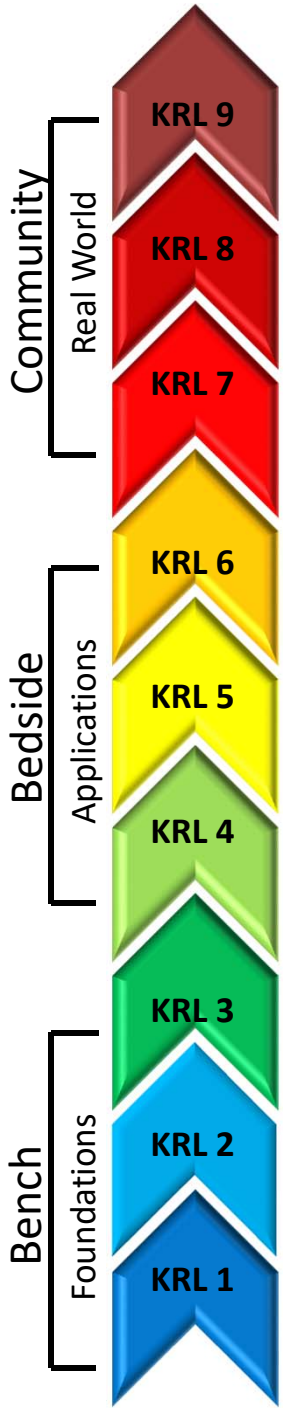


KRL7-9 ratings are given to KPs resulting from research designed to emphasize external validity (generalizability) of knowledge for use in a specified real world application context. This research often addresses a policy question, asking, "How does it compare to usual practice?" To achieve a rating of KRL7-9, the KP must be based on valid replicated KRL 4-6 research.

Examples include:

- Battlefield intervention
- Primary care screener
- Workplace prevention
- Systematic reviews of KRL 7-9 research
- Systematic reviews to inform creation of practice guidelines and study of a guideline

KP3 Community

KRL4-6 are given to KPs that seek to generate applied knowledge to eventually perform a non-research related function or to inform understanding of an application or tool. KRL4-6 research often asks questions such as "Can the application work under ideal research conditions?" and "(if the application can work), how does it work?" To achieve a rating of KRL 4-6, the KP must be based on valid, replicated KRL1-3 research.

Examples include:

- Applications that prevent, screen/diagnose, or treat illness
- Systematic reviews that summarize KRL4-6 research

KP2 Bedside

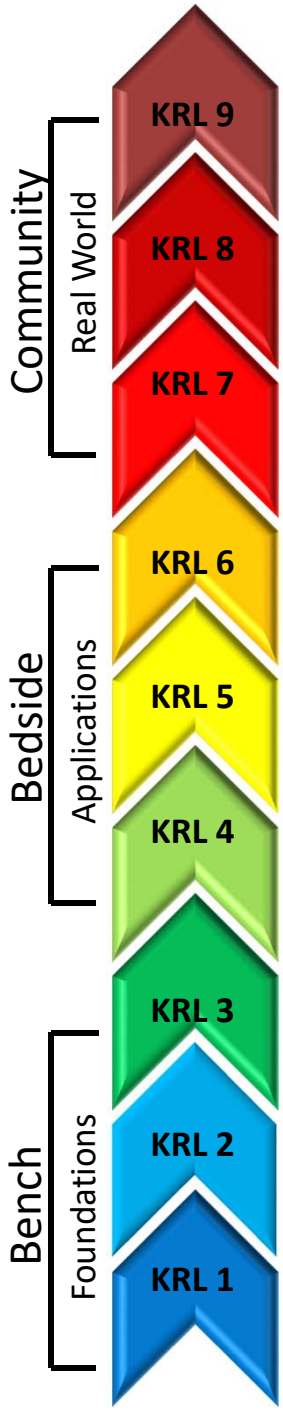
KRL1-3 provide the scientific foundation for KP development toward practical application. These KPs are the outputs of health research that seeks basic mechanisms rather than applications and tends to be theoretical or conceptual, often (but not always) comprising laboratory, descriptive, or exploratory studies.

Examples include:

- Animal research
- Non-Clinical laboratory research
- Descriptive epidemiology
- Systematic reviews of KRL1-3 research

KP1 Bench

Step 2: Determine the Knowledge Readiness Level (KRL)



KRL9 research replicates or reviews well-designed KRL7 and KRL8 studies (e.g., cost analyses to achieve desired effect; comparative effectiveness studies to aid context specific policy development or intervention decisions; systematic review to estimate effect size with average participants in a real world context, assess **"Does the application work?"** in a context, or determine for which participants or time period the application works in an identified context.)

KRL8 research expands on or replicates KRL7 studies to directly assess "Does the application work in the context of interest?" It uses valid designs with emphasis on external validity (generalizability) for an intended context. (e.g., multi-site to obtain average effects; generalizable analyses of real world, (e.g., administrative) data; usual or standard care (not placebo or contact time) controls; and average (not ideal) participants.)

KRL7 research comprises early studies adapting applications supported by KRL4-6 research for use in a military health context. (e.g., adaptation from a longer screener, feasibility and standardization for post-deployment use of a brief screener; initial multi-modal tests of combined KRL4-6 supported interventions to achieve improved outcomes in primary care; adaptation and initial study in military mental health settings of KRL4-6 support therapy for PTSD; adaptation and initial study of KRL4-6 supported protective gear for preventing TBI during deployment.)

KRL6 research replicates well-designed KRL5 studies. It adds nuance to answers from completed studies (e.g., not just "Can it work" and "How," but also "For whom," "Under what conditions," or "With what frequency?") It validates hypotheses that may suggest important application contexts (e.g., battlefield, primary care, emergency rooms, post-deployment screening). It includes systematic reviews of KRL4-5 studies to address "Can it work?" and "How?" questions.

KRL5 research tests *a priori* (pre-specified) hypotheses using rigorous scientific designs (e.g., RCTs for intervention efficacy) to directly assess "Can it work" and "If so, how?" It expands on or replicates a KRL4 finding and/or improves on the design of one or more KRL4 studies.

KRL4 research generates initial knowledge regarding a human health-related application or use. KRL4 findings require subsequent replication (e.g., descriptive human epidemiology or preliminary human studies, human studies that test a clinical hypotheses, pilot tests of an intervention, screening or diagnostic tool, and development of instrumentation needed to test an intended application (e.g., outcome measure).

KRL3 research validates hypotheses and hints at future applications, research that replicates or systematically reviews well-designed KRL1-2 studies or theory, descriptive studies, particularly involving animal research (e.g., tool for prediction, prognosis, screening, diagnosis, treatment, prevention)

KRL2 research expands on or replicates a KRL1 finding, including systematic review of KRL1 studies to formulate a theoretical model (e.g., animal studies that test a hypothesis or are the first true experiment on a nascent theory and human studies not based on animal study findings that are descriptive or hypothesis generating.

KRL1 research generates initial or very early scientific knowledge without regard to or indication of a specific health use. Its purpose is inferential, with the intention to generalize. Its findings require replication. (e.g., descriptive animal studies, or those that are hypothesis generating rather than hypothesis testing.)

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