BML 300: INTRODUCTION TO HEALTHCARE ENGINEERING

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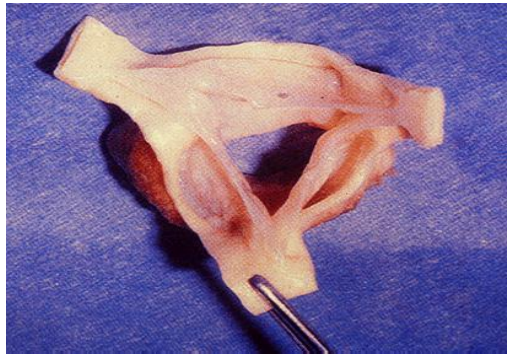
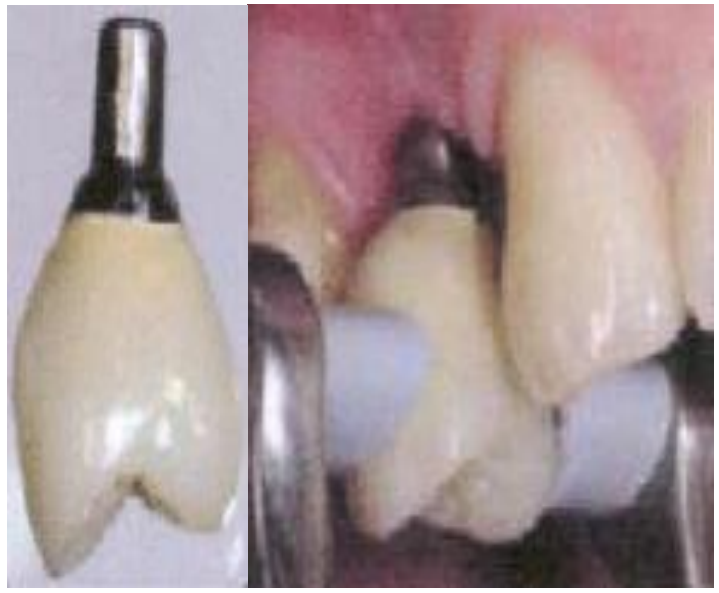
Date: Nov 11, 2024

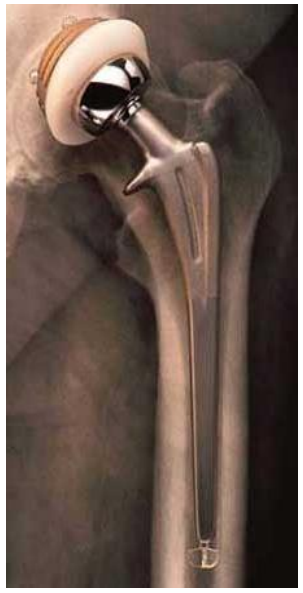
Medical Implants and Devices



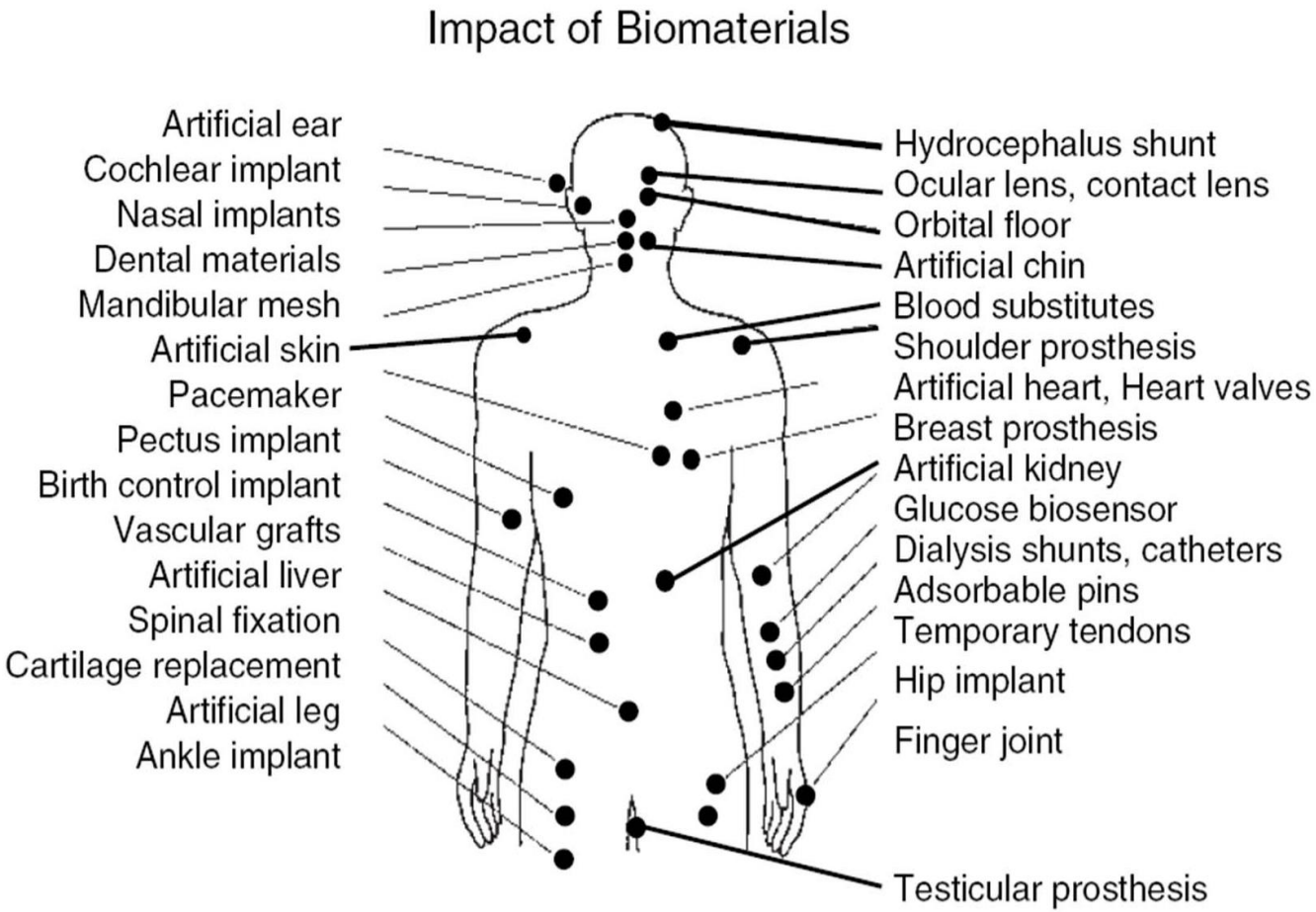
Bileaflet Heart Valves

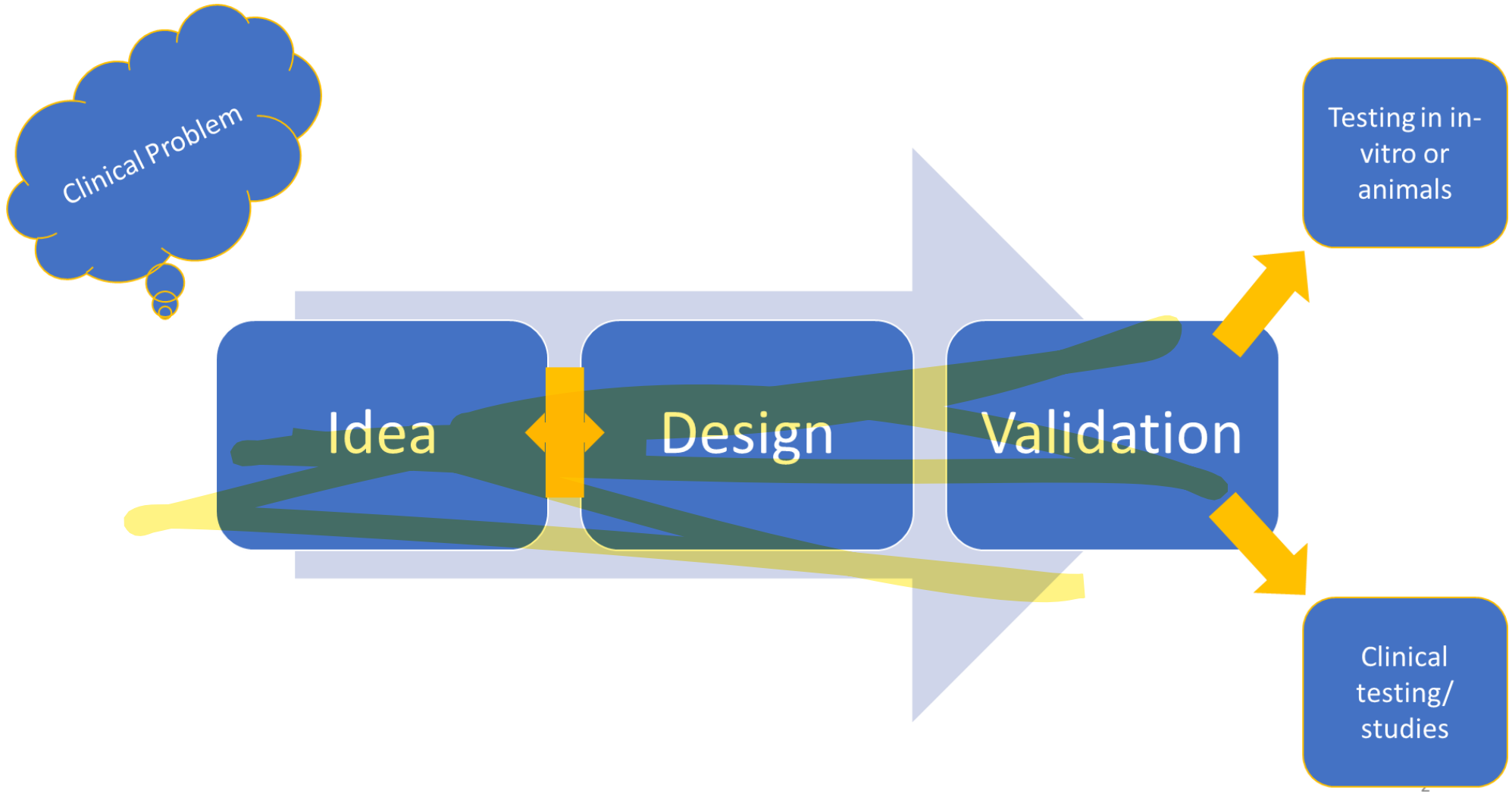


Dental Implants

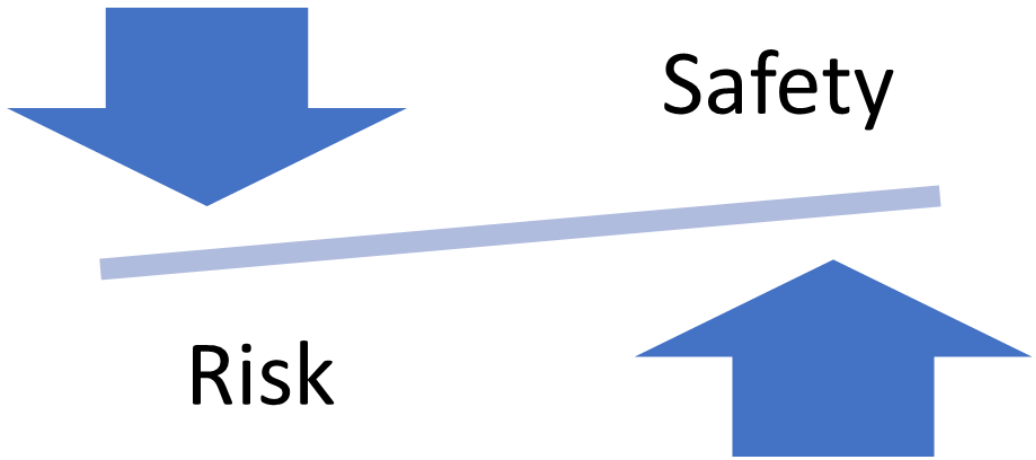


Hip Implant




Clinical Problem
Idea
Design
Validation
Testing in in-vitro or animals
Clinical testing/ studies

- Biomaterials and medical devices constitute an extremely diverse, heterogeneous category of items.
- Safety of medical device or a material is the primary concern of any inventor.



- Aim to translate biomedical engineering innovations from the lab to real-world applications.
- Possible only by proving the effectiveness in human subjects.

- Biocompatibility
- Surface characters
- Operator safety

Safety

- Not destroyed by autoclaving, dry heat, radiation, ethylene oxide, etc

Sterilizability

- Strength, durability
- Machinability, moldability, etc

Manufacturability

- Clinical trials
  - Translate
  - Evaluating the safety, efficacy, and performance
  - Optimize and refine

The responsibility lies with the regulators to ensure the safety and efficacy of medical devices.
A wide variety of items are classified as medical devices, making medical device regulations a complex procedure.
No standardized or universally accepted procedure till date

- Medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:
  - - recognized in the official National Formulary, or the US Pharmacopeia, or any supplement to them,
  - - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - - intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes

US FDA Section 201(h)

- All devices including an **instrument, apparatus, appliance, implant, material or other article, whether used alone or in combination, including a software or an accessory,** intended by its manufacturer **to be used specially for human beings or animals** which does not achieve the primary intended action in or on human body or animals by any pharmacological or immunological or metabolic means, but which may assist in its intended function by such means for one or more of the specific purposes of,-
- Diagnosis, prevention, monitoring, treatment or alleviation of any disease or disorder;
- Diagnosis, monitoring, treatment, alleviation or assistance for, any injury or disability;
- Investigation, replacement or modification or support of the anatomy or of a physiological process;
- Supporting or sustaining life;
- Disinfection of medical devices;
- Control of conception;

सत्यमेव जयते

MoHFW, New Drugs, Medical Devices and Cosmetics Bill, 2022

In-vitro diagnostic devices

In-vitro diagnostic device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination thereof intended to be used for examination and providing information for medical or diagnostic purposes by means of examination of specimens derived from the human bodies or animals

सत्यमेव जयते

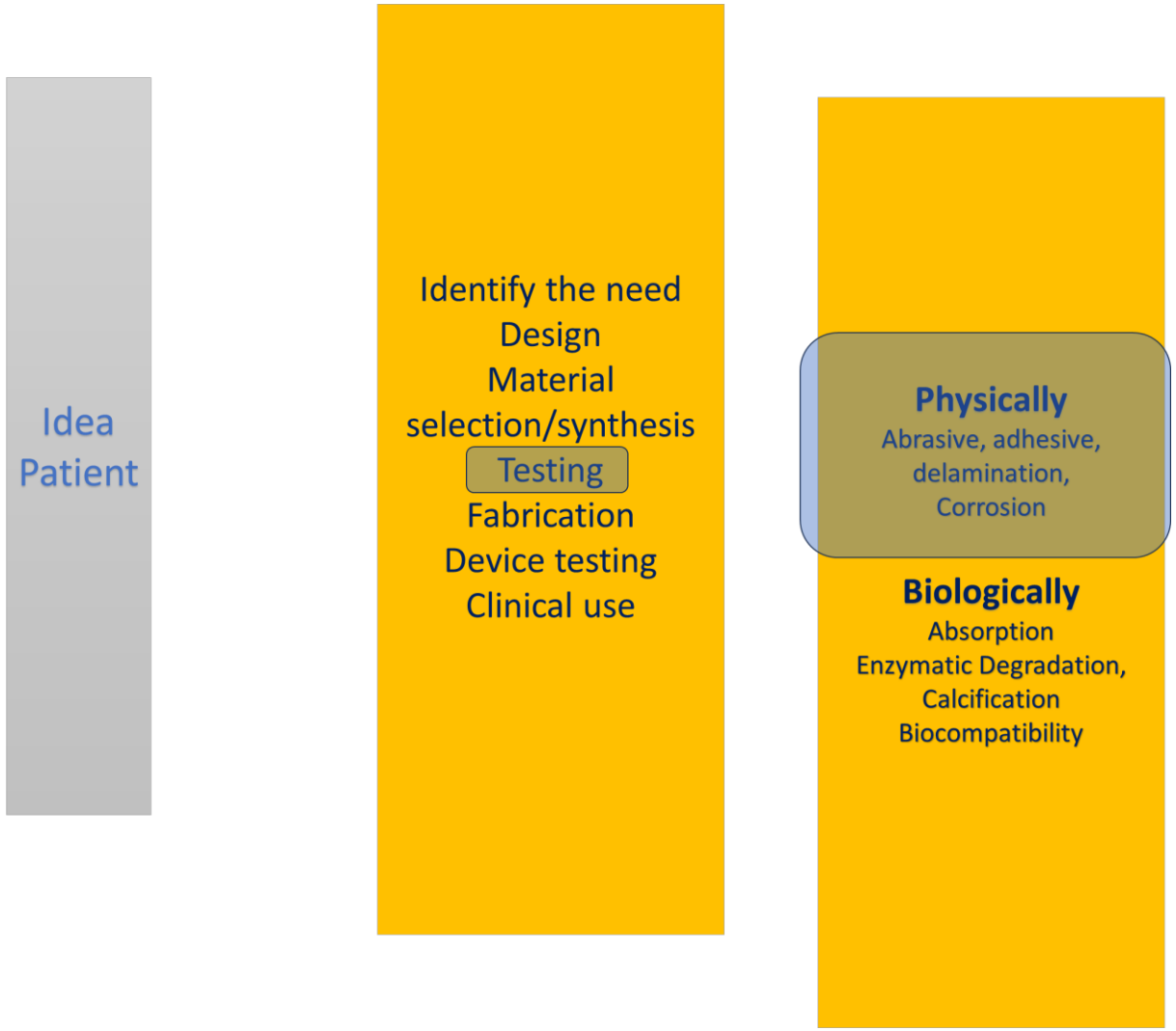
MoHFW, New Drugs, Medical Devices and Cosmetics Bill, 2022

Why not just pre-clinical testing

- Ultimately depends upon how the material is performing rather than how biocompatible it is.
- Biocompatibilty including other pre-clinical testings, still inadequate as a measurable quantity.
- But the ultimate effectiveness can only be established through clinical trials

Largely depends upon two factors

- How the host responds to the materials
- How the material responds to the host


Idea
Patient
Identify the need
Design
Material
selection/synthesis
Testing
Fabrication
Device testing
Clinical use
Physically
Abrasive, adhesive,
delamination,
Corrosion
Biologically
Absorption
Enzymatic Degradation,
Calcification
Biocompatibility

- Biocompatibility- The ability of a device material to perform with an appropriate host response in a specific situation.

DA's Biocompatibility Guidance on Use of ISO 10993-1

Screening tests

- Cytotoxicity
- Sensitization
- Irritation or intracutaneous reactivity
- Acute systemic toxicity
- Subacute toxicity
- Genotoxicity
- Implantation effect
- Hemocompatibility
- Chronic toxicity
- Carcinogenocity
- Reproductive and developmental toxicity
- Biodegradation

Bocompatibility test based on category and contact duration

Medical device categorization by			Biological effect												
Nature of Body Contact		Contact Duration													
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Surface device	Intact skin	A	X	X	X										
		B	X	X	X										
		C	X	X	X										
	Mucosal membrane	A	X	X	X										
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O			
	Breached or compromised surface	A	X	X	X	O	O								
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O	O		
External communicating device	Blood path, indirect	A	X	X	X	X	O				X				
		B	X	X	X	X	O	O			X				
		C	X	X	O	X	O	X	X	O	X	O	O		
	Tissue⁺/bone/ dentin	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Circulating blood	A	X	X	X	X	O		O^		X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		
Implant device	Tissue⁺/bone	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Blood	A	X	X	X	X	O		O	X	X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		

X = ISO 10993-1:2009 recommended endpoints for consideration*
O = Additional FDA recommended endpoints for consideration*
Note * All X's and O's should be addressed in the biological safety evaluation, either through the use of existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment.
Note ⁺ Tissue includes tissue fluids and subcutaneous spaces
Note ^ For all devices used in extracorporeal circuits
Note # Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, devices with relevant target populations (e.g., pregnant women), and/or devices where there is the probability for local presence of device materials in the reproductive organs.
Note @ Degradation information should be provided for any devices, device components, or materials remaining in contact with tissue that are intended to degrade.

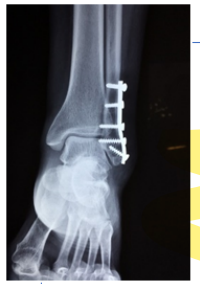
FDA's Biocompatibility Guidance on Use of ISO 10993-1. Accepted in MoHFW, Medical device act,2017

Classification of medical devices

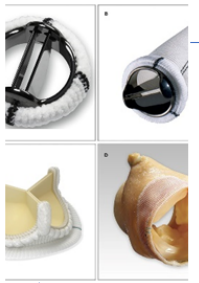
- Based on the anticipated risk while using the device.
- They are classified as—

CLASS A :-LOW RISK (Thermometer, tongue depressor)

CLASS B:-LOW-MODERATE RISK(Suction equipment, hypodermic needle)



CLASS C:-MODERATE-HIGH RISK(Ventillator,bone fixation plate)



CLASS D:-HIGH RISK(Heart valves, AICD)

MoHFW, Medical devices act,2017

Need v/s necessity

- Similar to pre-clinical testing, not all medical devices need to go through all the stages of clinical trials.
- Depends upon the classification of medical device.
- Depends upon the ability of existing data to adequately address the benefits/risk profile, claims and side effects of a medical device.
- Mostly the implantable devices i.e. Class III 7 Class IV need to go through all stages of trials.
- The ultimate decision lies with the legal authorities.

Clinical investigation

- A systemic investigation or study in one or more human subjects, undertaken to access the safety, clinical performance, and/or effectiveness of the product.

Why?

- Ensure patient safety by rigorously assessing the potential risks and benefits of new interventions.
- Clinical testing help optimize the performance and usability of biomedical innovations.
- It serves as a bridge between academia, industry, and healthcare institutions.
- Collaboration between researchers, engineers, clinicians, and regulatory bodies for the successful translation of biomedical engineering innovations into clinical practice.
- Helps in gaining practicality and acceptance of new devices

	Pharmaceutical products	Medical devices
Types of organisations which bring products to market	Mostly large and established pharmaceutical companies	Variable: many start-ups and small and medium enterprises, as well as large medical technology companies
Time when clinical evidence is generated	Generally pre-market	Both pre- and post-market studies
Clinical development phases	Highly standardised (phases 1–4)	Less standardised Product-dependent
Clinical study design	Highly standardised Double-blind randomised controlled trial expected	Less standardised Pivotal trials often done after CE-marking
Irreversible effects on study subjects	Rare	Common, particularly with permanent implants

Regulations in India

- Chapter VII of Medical device act, 2017 deals with the regulations of Clinical Investigation of Medical Device And Clinical Performance Evaluation of New In vitro Diagnostic Medical Devices.
- Permission needs to be taken from Central licensing authority.
- Permission needs to be taken for both Pilot investigation and pivotal investigation.
- Medical devices claiming substantial equivalence to predicate devices shall not be marketed before getting the approval.

IDEAL-D framework for implantable devices

- Idea, Development, Exploration, Assessment, Long term study
- Introduced for developing and evaluating new surgical procedures
- Broadly divided into four stages
  - Stage 0-Preclinical
  - Stage 1-first in human
  - Stage 2-Prospective developmental studies
  - Stage 3- Randomised control trials or alternatives
  - Stage 4-Long term studies

Sedrakyan, A., Campbell, B., Merino, J. G., Kuntz, R., Hirst, A., & McCulloch, P. (2016). IDEAL-D: a rational framework for evaluating and regulating the use of medical devices. BMJ (Clinical research ed.), 353, i2372.

Stage 0- Preclinical stage

- Product design, materials, and functional components are determined and tested to prepare the device for first-in-human (stage 1) studies.
- Animal models are often used to optimise new techniques before human studies begin.
- The principles for stage 0 reporting will have to balance the need to protect intellectual property and prove that appropriate ex-vivo tests of safety and reliability have been conducted.

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Stage 1- First in human

- Universal registration of studies could allow the identification of benefit and harm themes and trends by surveillance of incoming reports and detect possible device harms at an early stage, ensuring that unsuccessful innovation is not repeated through ignorance.
- Innovators should be ethically obliged to search the registry before embarking on a first-in-human study to avoid repeating a harmful error reported by another investigator.
- But, how to protect reports of device innovations that proved harmful from being used for legal challenges?
- A preventive measure is to spend a good time in stage 0 and conduct vigorous and rigorous pre-clinical trials.

Sedrakyan, A., Campbell, B., Merino, J. G., Kuntz, R., Hirst, A., & McCulloch, P. (2016). IDEAL-D: a rational framework for evaluating and regulating the use of medical devices. BMJ (Clinical research ed.), 353, i2372.

Stage 2- Prospective developmental studies

- Most technical device iterations occur during stages 0-1 and involve a single manufacturer.
- Consensus among the medical professionals is not an issue with medical devices at this stage.
- A stage 2 aims, through prospective exploration studies, at facilitating progression to definitive randomised controlled trials in stage 3.
- Can be called as a extended pilot study.
- Requirement for a stage 2 study would considerably enhance the average level of clinical evidence supporting new devices and would “set up” such devices for a definitive study.

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Pilot investigation and pivotal investigation

Pilot

- clinical investigation to be carried out for the first time in human participants
- Exploratory in nature
- Small number of participants
- Assessing feasibility, eligibility, potential harm, validating outcome method

Pivotal

- After data anaylsis from pilot study
- Definitive and confirmatory
- Larger participants
- Assess safety and efficacy

	PRE-MARKET			POST-MARKET	
Clinical Stage	Pre-Clinical	Pilot	Pivotal	Post-Market Surveillance (PMS)	
Type	Exploratory	Exploratory & Confirmatory	Confirmatory		Observational
Descriptors	 - In-Vitro - In-Vivo	 - First-in-Human - Pilot Study - Exploratory Study - Early/Traditional Feasibility Study - Proof-of-Concept - Investigator Initiated*	 - Pre-Market CI - Pivotal CI - "Phase 3" Study	 - Post-market CI - Investigator Initiated* - PMCF Study - Post-Approval Study (PAS)	 - Post-Market CI - PMCF Study - Investigator Initiated* - Registry - Survey - Case Series - Cohort Study - Postmarket Surveillance Study
Burden to Human Subject		**Interventional**			**Non-Interventional**

Stage 3- RCTs

- Practical considerations are likely to lead regulators and policymakers to define a limited category of devices for which stage 2 studies and stage 3 randomized controlled trials will be required.
- The evidence that inadvertent patient harm can result from apparently small modifications to existing devices suggests that a clinical trial should normally be required for most implantable devices.

Sedrakyan, A., Campbell, B., Merino, J. G., Kuntz, R., Hirst, A., & McCulloch, P. (2016). IDEAL-D: a rational framework for evaluating and regulating the use of medical devices. BMJ (Clinical research ed.), 353, i2372.

Stage 4-Long term studies

- Post-market surveillance studies may be conducted for a number of reasons, including to confirm the safety and efficacy of the device once it's on the market or to answer questions about the long-term safety or performance of the device.
- Prospective registries were started from the outset of clinical use they could be used continuously for safety surveillance of higher-risk devices, picking up weak signals from rare events and outlier device reports as technology proliferates.

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- ISO 14155: 2011 Clinical Investigation of Medical Devices for Human Subjects —Clinical investigations must take into account scientific principles underlying the collection of clinical data along with accepted ethical standards surrounding the use of human subjects.
- A properly conducted clinical investigation, including compliance to the clinical investigation plan and local laws and regulations, ensures the protection of human subjects, the integrity of the data and that the data obtained is acceptable for the purpose of demonstrating conformity to the Essential Principles.

Ethics

- It should generate new data and answer specific safety, clinical performance, and effectiveness questions that remain unanswered by the current body of knowledge.
- The desire to protect human subjects from unnecessary or inappropriate experimentation must be balanced with the need to protect public health through the use of clinical investigations where they are indicated.

Designing a clinical trial

- Clear statement of the objectives
- Minimizing the risk to the subjects
- Defining the adverse events
- Defining the study outcomes or endpoints
- Appropriate subject population
- Sampling strategy
- Measures to minimise the bias
- Identifying the confounding factors
- Selecting the appropriate controls/comparator device(active controls, historic controls)
- Study design(parallel, cross over, single arm, cohort)
- Type of comparison(superiority, non inferiority, equivalence)
- Follow up duration and monitoring

- The gold standard of study design for clinical trials is a randomised controlled trial, preferably with blinding and a placebo as the control.
- To brush up
  - **Controlled** means that there is a control group of participants who receive no treatment, a placebo, or some other treatment (comparison study);
  - **Randomised** means that trial participants are randomly assigned to either the treatment group or the control group;
  - **Blinding** means that participants don't know which treatment they are receiving (single-blinded), and in some studies, neither do the doctor(s) or study coordinators (double-blinded).

Clinical trials for medical devices

Controlled studies	• Device v/s no device • Device v/s gold standard device • Device v/s standard care/physical therapy
Blinding	• Usually difficult • The evaluator, statistician can be blinded
Randomisation	• Can be done • Patient consent can be a roadblock