Collaborative Engineering

Clinical Trials - TKP

- Classification – Controls
- Typical Clinical Trials
- Phases
- Application – TKP

OrthoCAD Lab, I.I.T. Bombay

Medical Devices – Classification

Class I – Low Risk

- General controls are sufficient
  - to provide reasonable assurance of the safety and effectiveness
- Examples: elastic bandages, examination gloves, and hand-held surgical instruments

General Controls

- Prohibition against adulterated or misbranded devices
- Premarket notification 510(k) requirements
- Good Manufacturing Practices (GMPs)
- Labeling
- Registration of manufacturing facilities
- Listing of device types
- Record keeping
- Repair, replacement or refund

Medical Devices – Classification

Class II – Medium Risk

- General controls alone are insufficient
  - to assure safety and effectiveness
  - existing methods available for such assurances
- Subject to special controls
- Examples: powered wheelchairs, infusion pumps, and surgical drapes

Special Controls

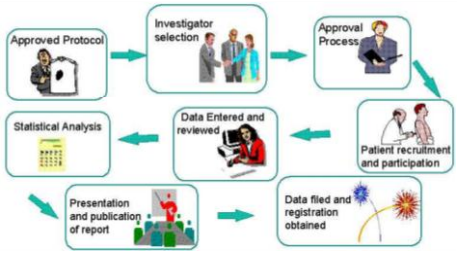
- Performance standards (discretionary, voluntary national or international standard, recognized by rulemaking)
- Post-market surveillance
- Patient registries
- Development and dissemination of guidelines/guidances
- Design controls
- Recommendations and other appropriate actions
- Tracking requirements

Medical Devices – Classification

Class III – High Risk

- Insufficient information exists
  - to derive general & special controls are sufficient
  - to provide reasonable assurance of the safety and effectiveness of such devices
- Such devices are:
  - Life sustaining or life supporting
  - Substantial importance preventing impairment of human health
  - or unreasonable risk of illness or injury

Typical Clinical Trials – History



- 1628: therapeutic trial, bloodletting for fevers
- 1747: trial of oranges & limes for scurvy
- 1988 - Clinical trials (new drug) made mandatory in India

Clinical Trials Classification

Drug Clinical Trials

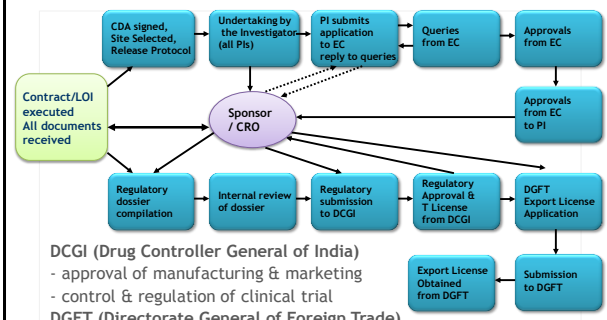
- Treatment trials – Treat disease
- Prevention trials – Prevent disease
- Early-detection trials/screening trials
- Diagnostic trials – better diagnosis
- Quality-of-life studies/supportive care studies – improve

Drugs – Medical Devices

The Ministry of Health (Gazette not. S.O.1468 (E)-6/10/2005) declared the following STERILE DEVICES as DRUGS
Section 3 (b) (iv)

1. Cardiac Stents.
2. Drug Eluting Stents.
3. Catheters.
4. Intra Ocular Lenses.
5. I.V. Cannulae.
6. Bone Cements.
7. Heart Valves.
8. Scalp Vein Set.
9. Orthopedic Implants.
10. Int. Prosthetic replacements.

Regulatory & IRB Approval Process: India



DCGI (Drug Controller General of India)
- approval of manufacturing & marketing
- control & regulation of clinical trial

DGFT (Directorate General of Foreign Trade)
- permission export of patient samples

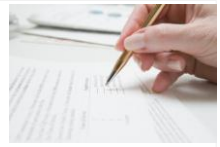
Phases Clinical Trials – Drugs

Phase	No. of Subjects	Goal
Pre - Marketing		
Phase I	20-80	Evaluate Safety, Safe dosage
Phase II	100-300	Effectiveness, Further safety
Phase III	1000-3000	Confirm effectiveness, Monitor side effects, compare
Post Marketing		
Phase IV	>3000	Additional info., Risks, benefits & optimal use

Phases Clinical Trials – Medical Devices

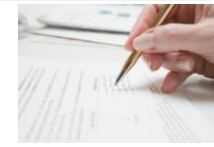
Phase	Primary Intention	Desired Outcomes
First in human Studies	• Feasibility of device, • "No Additional Risk" • Performance in target condition • Demonstration, lowest risk	Non-inferior performance over control arm No Additional risk over control arm
Pivotal Studies	• Safety & efficacy of • Performance in target condition	"Safe for wider human use"
Post marketing surveillance	Evaluation of Device in more defined / Difficult subgroups	Performance & safety in extended cond^{n}, Marketing tool

Clinical Trials – Application



- Background and Introduction
- Protocol/ Study Number
- Study Rationale & Objectives
- Study Design
  - Overview of the Study Design
  - Flow chart of the study
  - brief description methods and procedures
  - Discussion of Study Design
- Study Population
- Subject Eligibility
  - Inclusion Criteria
  - Exclusion Criteria

Clinical Trials – Application



- Study Assessments
- Study Conduct
- Study Treatment
- Adverse Events
- Ethical considerations
- Study Monitoring and supervision
- Investigational product management
- Data Analysis
- Undertaking by the investigator

Collaborative Engineering

Clinical Trials – Example TKP

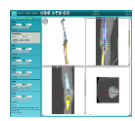
Clinical Trials – TKP

- Study Title
  - "To evaluate a new indigenous rotating hinge distal femur prosthesis (developed under Ortho-CAD project) for reconstruction of tumor defects."

Clinical Trials – TKP

- Protocol/ Study Number – NA
- Rationale – demonstrate safety & functional efficacy TKP
- Objective
  - To evaluate new prosthesis for function, extracortical bridging and ease of implantation
  - To evaluate and evolve the armamentarium
  - To evaluate and evolve the virtual implantation software

Novel Surgical Instruments



OrthoSYS: 3D surgery planning software

TKP Clinical Trials – Investigators

Institute	Investigators	Cases to be Accrued
Group I Tata Memorial Hospital	**Dr Manish Agarwal** Dr Ajay Puri	**50**
Group II AIIMS	Dr Shishir Rastogi	**20**
Group III		**30**
Sanchayeti Hospital	Dr Yogesh Panchwagh	
RCC Trivandrum	Dr Subin Bhaskar Dr Gopalkrishnan	
Ramaiyah Medical College	Dr Srinivas CH Dr Sundaresh	
Gujrat Cancer Research Institute	Dr Mandip Shah	

Clinical Trials – TKP

Begins with TMH Accrual of 20 cases	• Design and instrumentation finalised during this stage • small inventory till design final
Others Centres start accrual	• Design and instrumentation finalised • inventory of 150 cases • Interim analysis after 50 cases
Completion of accrual	• additional accrual for more data • accrual till 200 cases or till permission for final manufacture

TKP Clinical Trials – Subject Eligibility

Inclusion Criteria

- Patients with primary malignant bone tumors around knee
- Patients with non metastatic disease.
- Tumor amenable to resection with adequate margins
- Possible to retain adequate limb function after resection and reconstruction
- Expected ultimate function is superior
- Patient is undergoing appropriate adjuvant therapy
- Informed consent from patient or parents as appropriate

TKP Clinical Trials – Subject Eligibility

Exclusion Criteria

- Patients with metastatic disease
- Tumor not amenable to resection with adequate margins
- Ablative surgery function superior to limb salvage
- Patient not undergoing appropriate adjuvant therapy
- Patient unwilling in the trial with new implant
- Patient unwilling or unreliable to follow up.

TKP Clinical Trials – Assessment

Points	Pain	Function	Emotional acceptance	Supports	Walking ability	Gait
5	None	No restriction	Enthused	None	Unlimited	Normal
4	Intermediate	Intermed.	Intermed.	Intermed.	Intermed.	Intermed.
3	Modest, non disabling	Recreational restriction	Satisfied	Brace	Limited	Minor cosmetic alteration
2	Intermediate	Intermed.	Intermed.	Intermed.	Intermed.	Intermed.
1	Intermittent narcotics	Major disability	Accepts	One cane or crutch	Inside only	Major cosmetic
0	Severe, continuously disabling	Total occupational restriction	Dislikes	Two canes or crutches	Not independent	Major handicap

SUMMARY

- Manufacturing Feasibility
- Concept Elimination
- Geometry changes
- Functioning can affect mfg – surface finish