

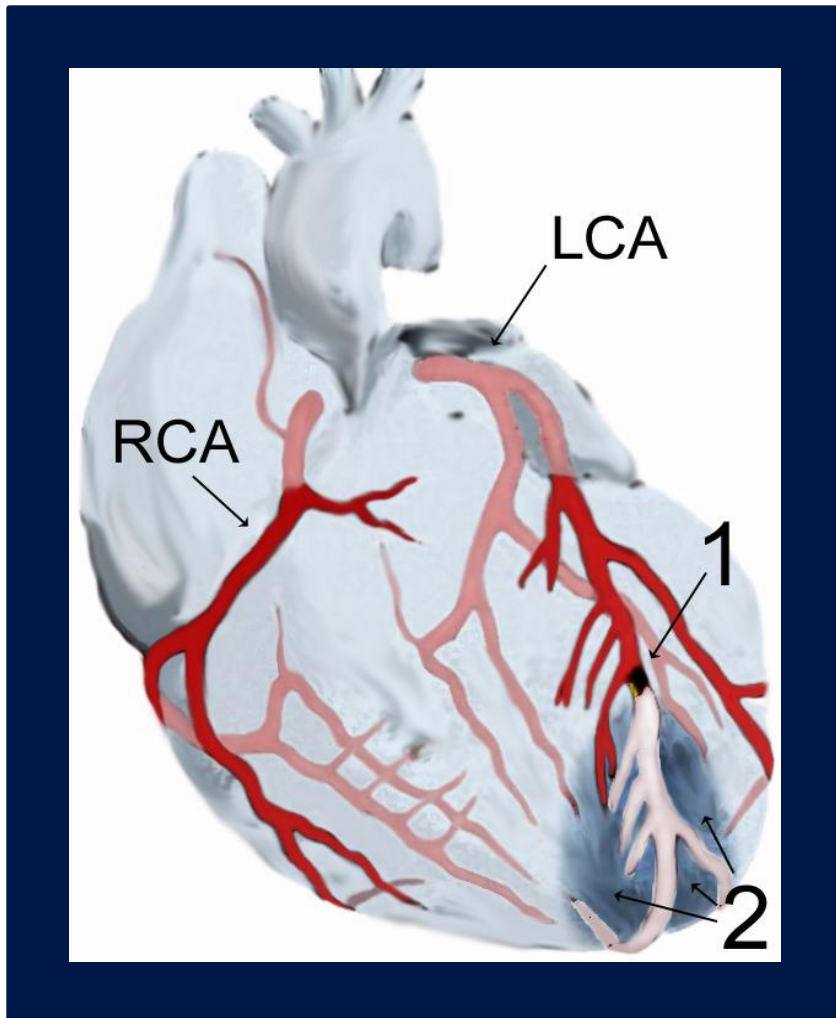


Two Arm, Double Randomised Post Market Study

Dr Sunita Ahir, Regulatory Affairs Manager

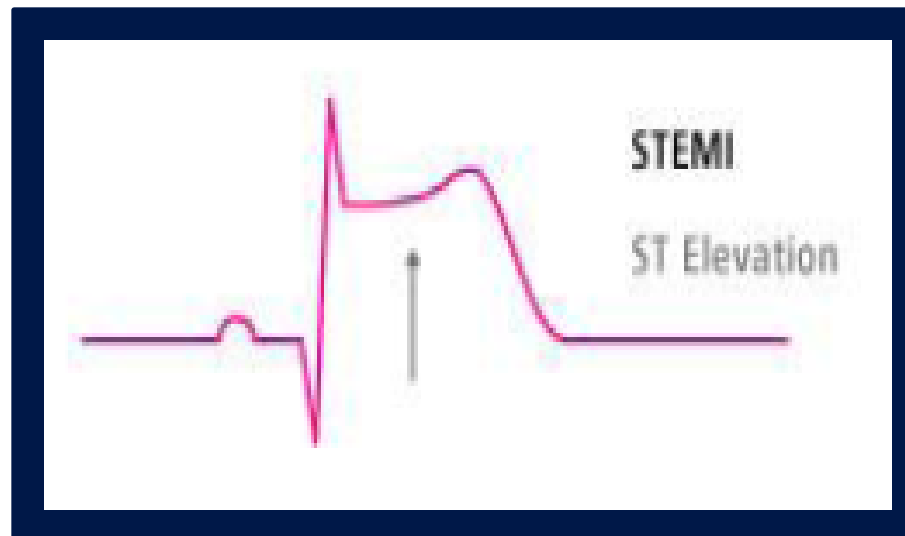
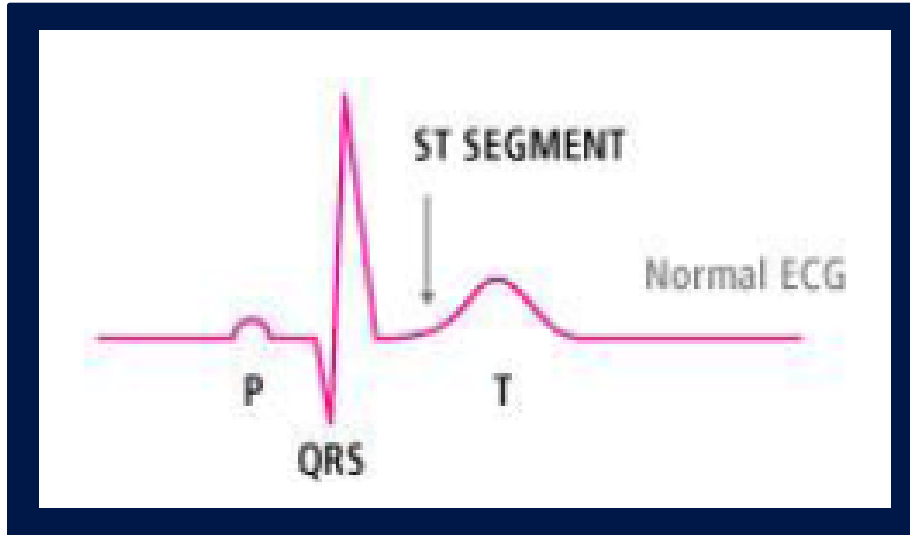
October 2011

Myocardial Infarction



Acute Myocardial Infarction (**AMI** or **MI**), more commonly known as a **heart attack**, is a medical condition that occurs when the blood supply to a part of the heart muscle or myocardium is interrupted. It is a medical emergency, and the leading cause of death for both men and women worldwide, particularly in developed countries.

Myocardial Infarction



STEMI

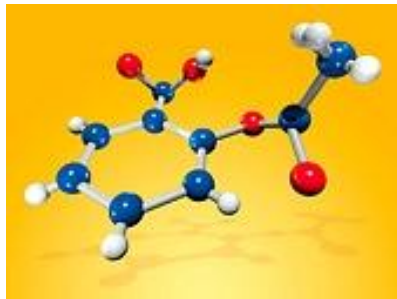
Current treatment options:

- Anticoagulants
- Percutaneous Coronary Intervention
- Or both

Case Study

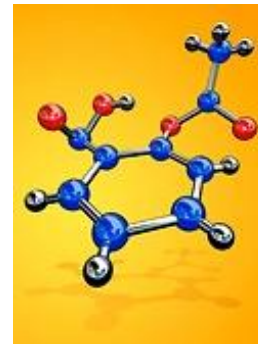
A dual arm double randomized trial in patients with STEMI comparing:

1) **ARM 1:**



A

Anticoagulant A

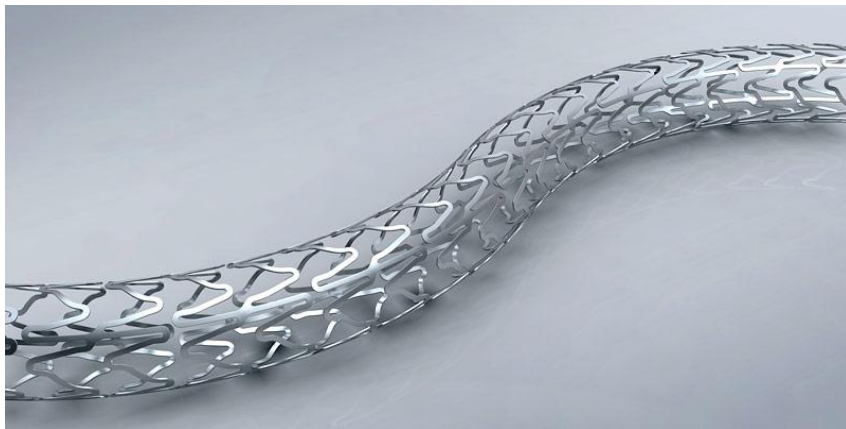


B

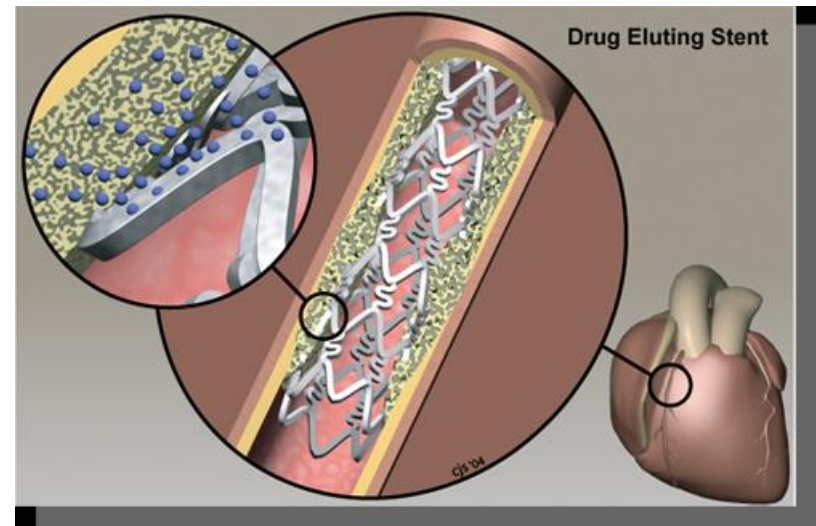
Anticoagulant B

Case Study

- 2) **ARM 2: Stent implantation** with a Drug Eluting Stent to an otherwise identical bare metal stent



C
Bare Metal Stent



D
Drug Eluting Stent

Study Design

- Drug and device commercialized but investigational for the intended use
- 3,400 randomized patients with ST segment elevated AMI (within 12 hours of symptoms onset) in whom a primary PCI strategy was intended
- Prospective, single blind, multi-center trial with FDA approval
- Participating countries: North and South America, Europe and Israel

Study Design

Problems with US + OUS protocols

Bram Zuckerman FDA Division of Cardiovascular Devices, CDRH

Clinical studies should adhere to the fundamental Principles of Good Clinical Practise:

- Protection of human subjects
- Trial design and execution that produces high quality data
- Documentation that can be verified on inspection

Study Design

Problems with US + OUS protocols

Bram Zuckerman FDA Division of Cardiovascular Devices, CDRH

- **Protocols missing essential elements:**
 - Study endpoints
 - Detailed inclusion/exclusion criteria
 - Subject follow up schedule
 - Lack of independent clinical event committees, safety monitoring boards, core labs
 - Monitoring of source documents and accounting for protocol deviations
 - Long term follow up beyond the endpoint was missing
 - Stats plan for combining US and OUS data

Study Design

- **The protocol detailed:**
 1. Regulatory requirements
 2. Criteria for Evaluation – primary and major secondary endpoints for the pharmacology and stent arms of the study
 3. Inclusion/Exclusion Criteria
 4. Details of :
 - Core Labs
 - Data Safety Monitoring Board
 - Clinical Events Committees
 5. Statistical methods
 6. Follow-up schedule

Study Design

- Pharmacology Arm – 30 days
- Primary Endpoint:
 - The composite of major adverse ischemic events and major bleeding (net clinical benefit endpoint)
- Major Secondary Endpoints:
 - Major adverse ischemic events (death, reinfarction, stroke or ischemic target vessel revascularization)
 - Major bleeding

Study Design

- Stent Arm – 1 year
- Primary Efficacy Endpoint:
 - Ischemic target lesion revascularization
- Primary Safety Endpoint:
 - The composite rate of death, reinfarction, stent thrombosis or stroke
- Major Secondary Endpoint (13 months):
 - Binary restenosis (angiographic subset)

Regulatory Requirements

- The study was conducted in compliance with:
 - the CIP (protocol),
 - the sponsor`s standard operating procedures,
 - the United States Food and Drug Administration requirements
 - [local regulations where applicable](#)
 - the International Conference on Harmonisation (ICH) GCP guidelines
 - the Declaration of Helsinki

Role of CRO: Outside US study

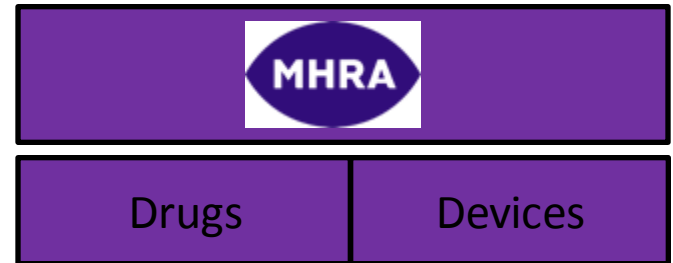
- The OUS study was contracted out to D-Target (Premier Research acquired D-Target in June 2007).
- D-Target responsible for submissions, Project management, Study set-up, site assessment, monitoring and safety reporting in the EU.
- D-Target enlisted a subcontractor for work carried out in Israel.



European Union



European Union: Member State Structure

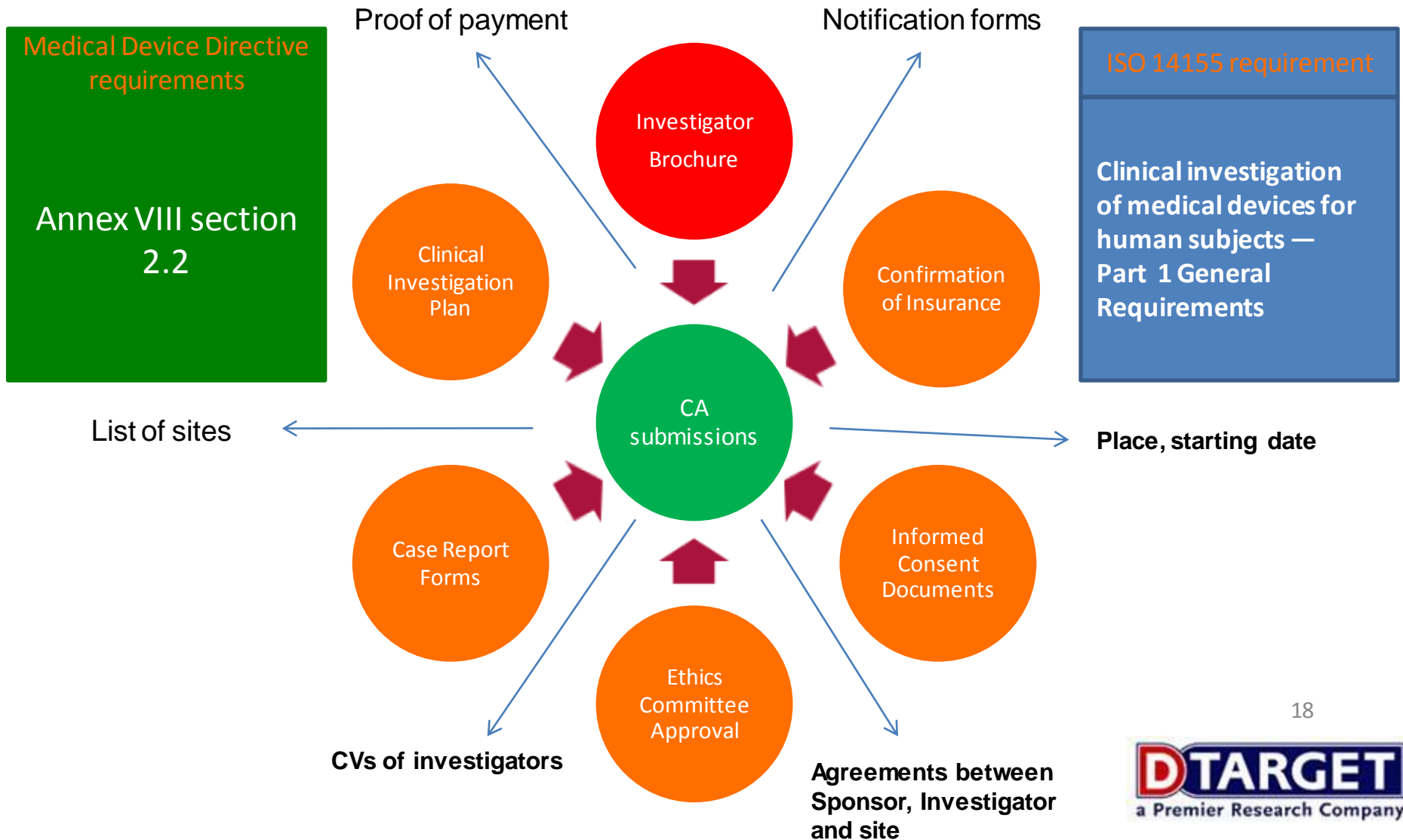


European Union: Clinical Trial Requirements

- Clinical Trials must be approved by Ethics Committees/Competent Authorities before the start of the trial

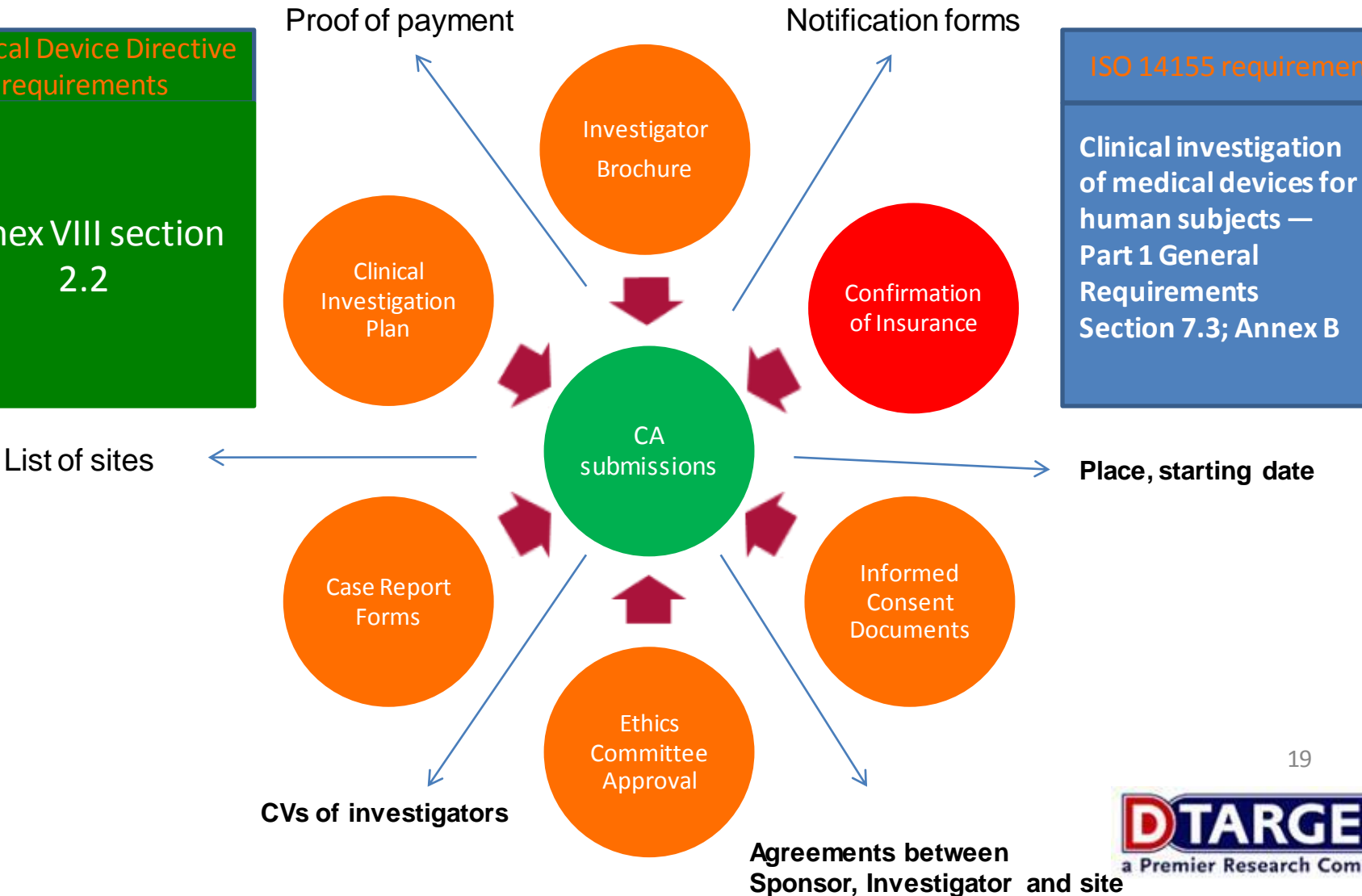
Medical Devices Directive: Article 15, Annex VIII;
ISO 14155 part 1 section 6.6

Device Clinical Trial Submissions: Competent Authority requirements

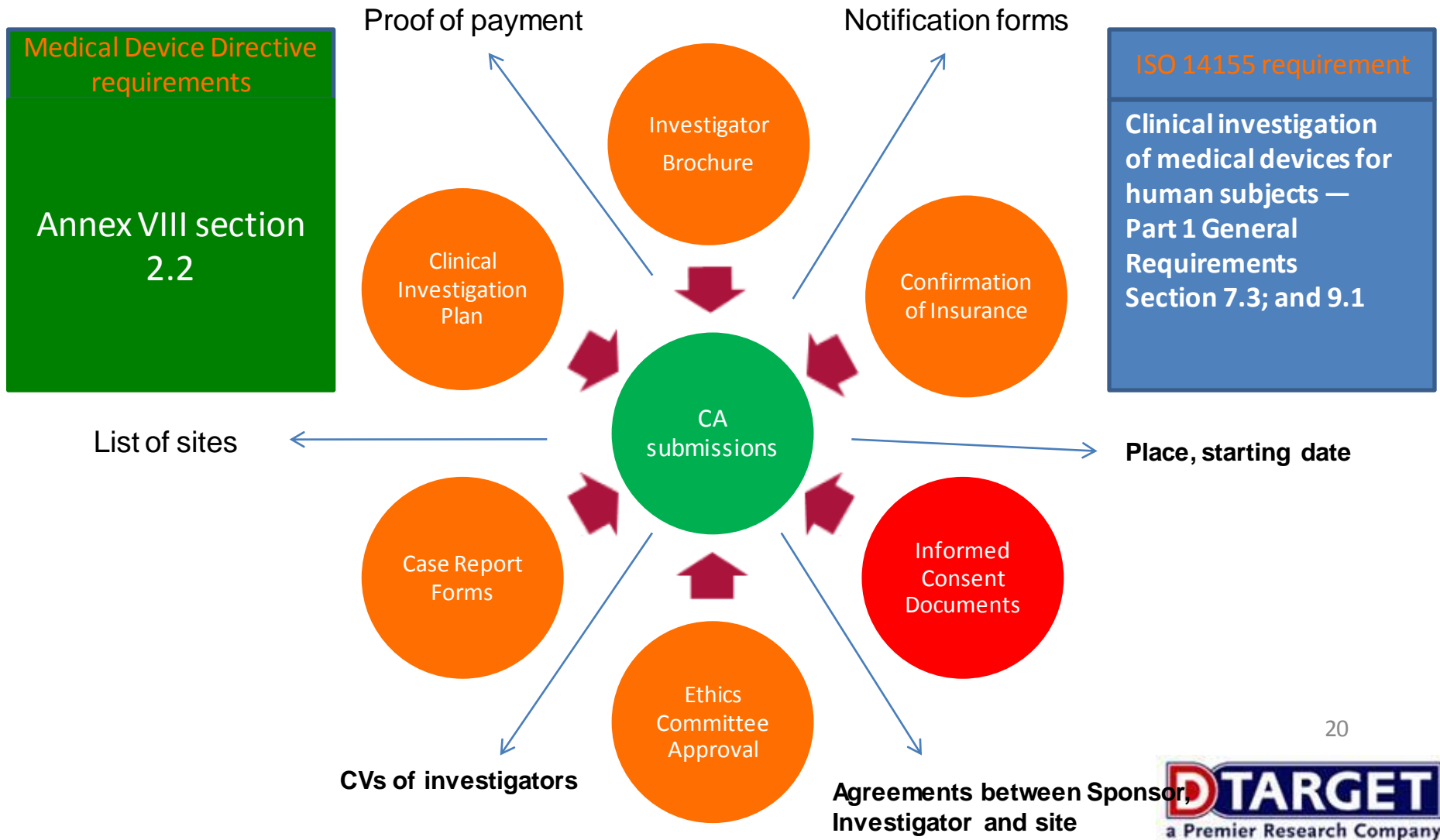


Device Clinical Trial Submissions: Competent Authority requirements

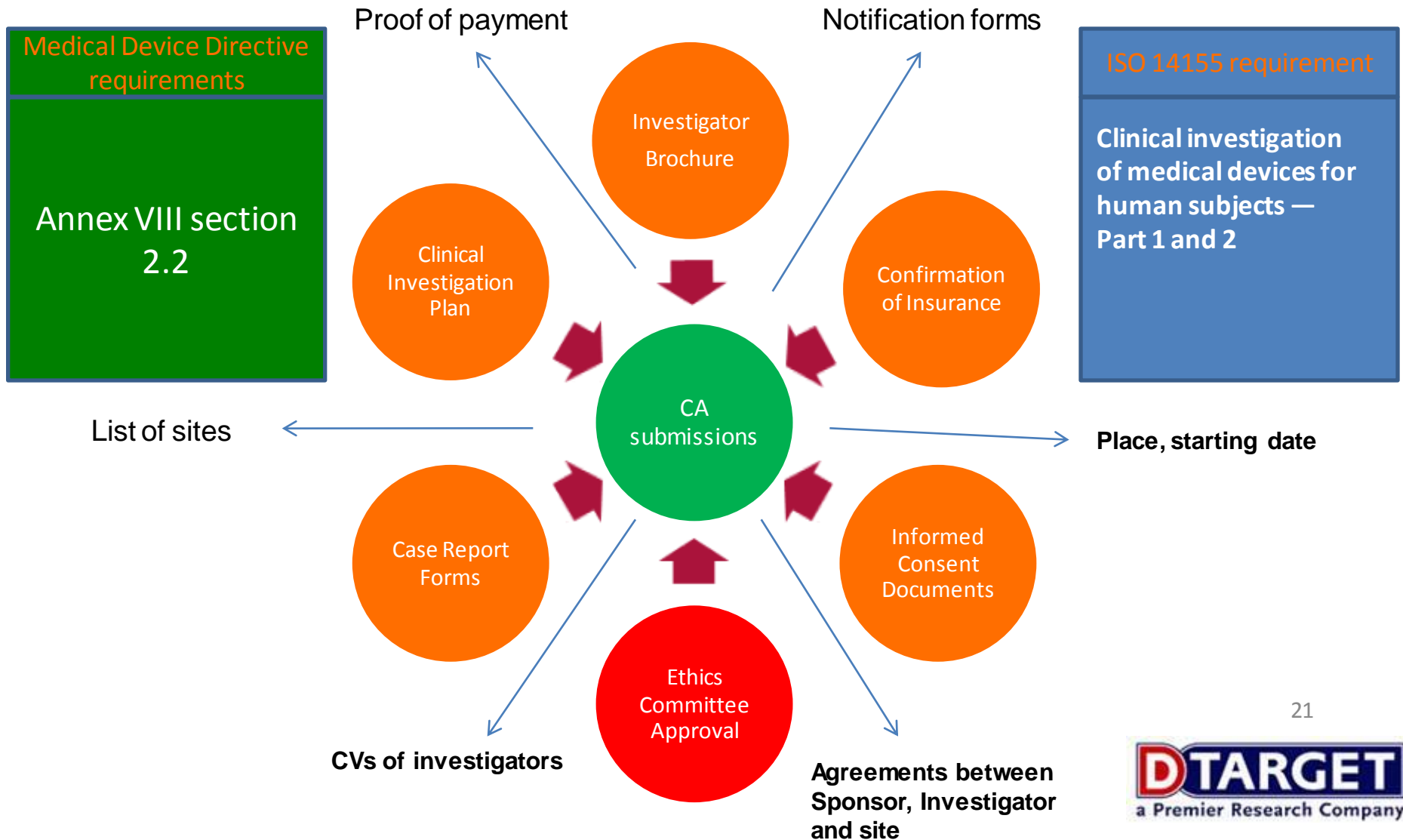
Medical Device Directive requirements
Annex VIII section 2.2



Device Clinical Trial Submissions: Competent Authority requirements



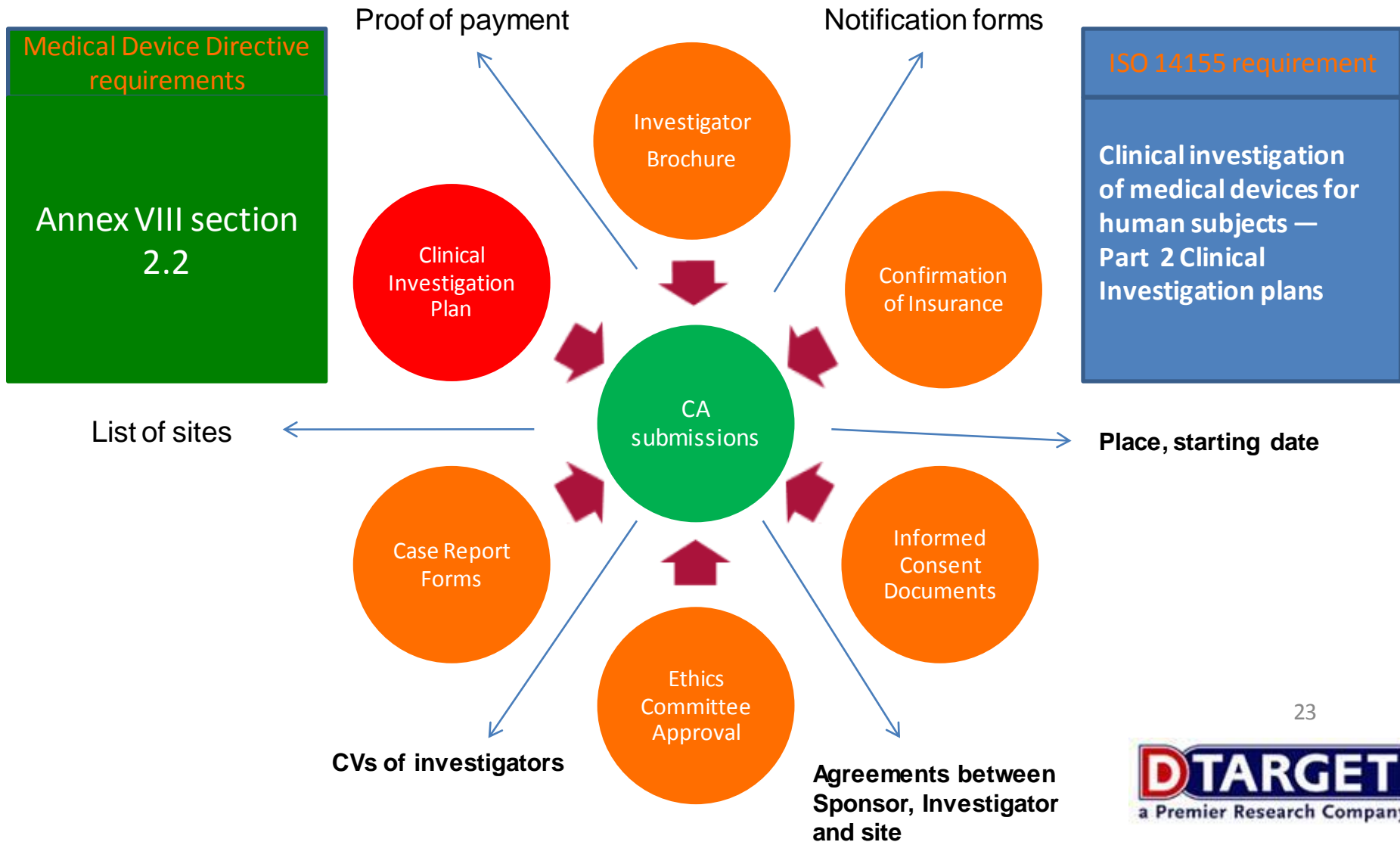
Clinical Trial Submissions: Competent Authority requirements



Device Clinical Trial Submissions: Competent Authority requirements

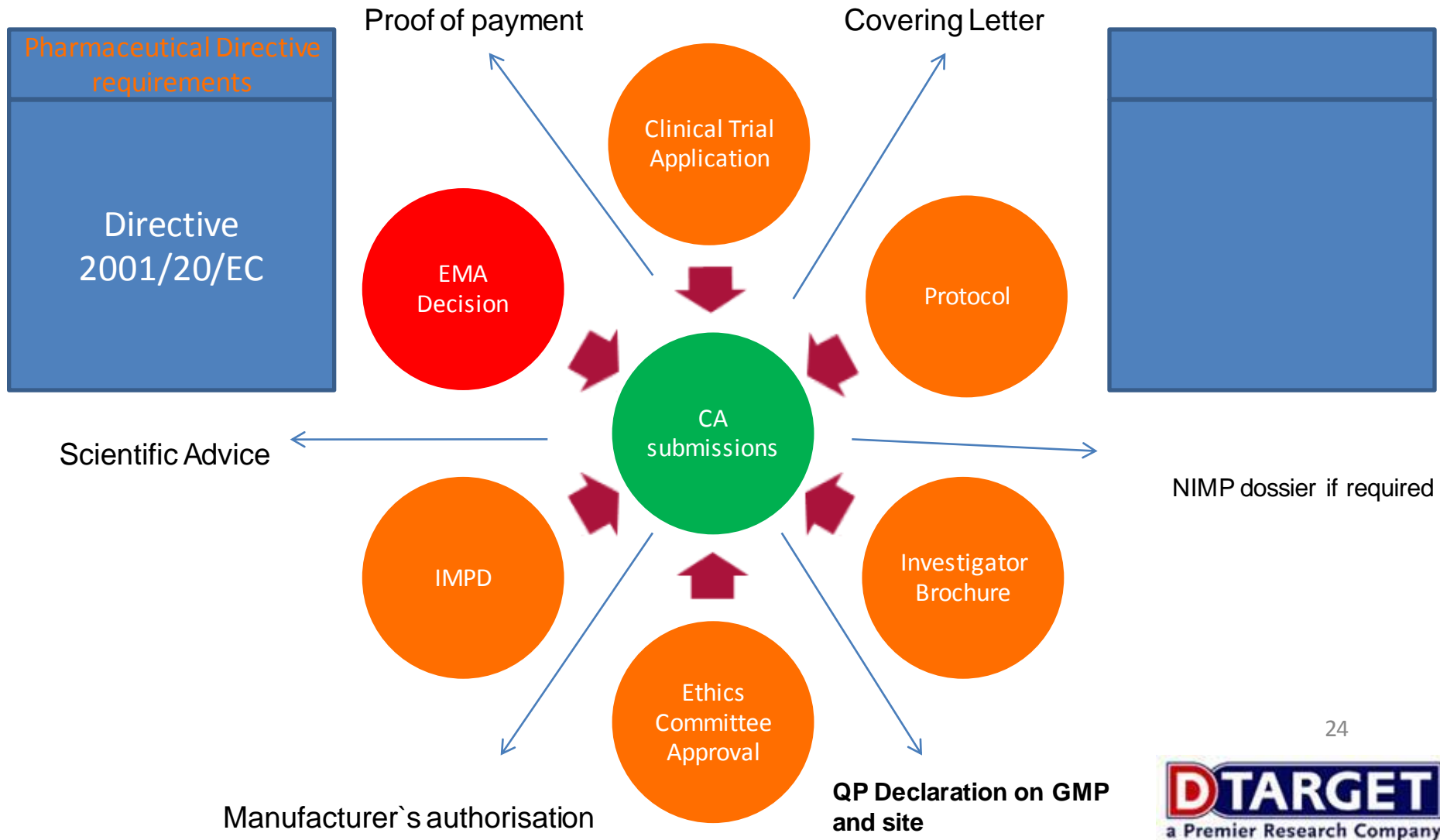


Device Clinical Trial Submissions: Competent Authority requirements



Drug Clinical Trial Submissions

Competent Authority requirements



Drug and Device Clinical Trial Submissions: Ethics Committees



European Union: similar but different!

Data

Protection:

Required in

France

Netherlands

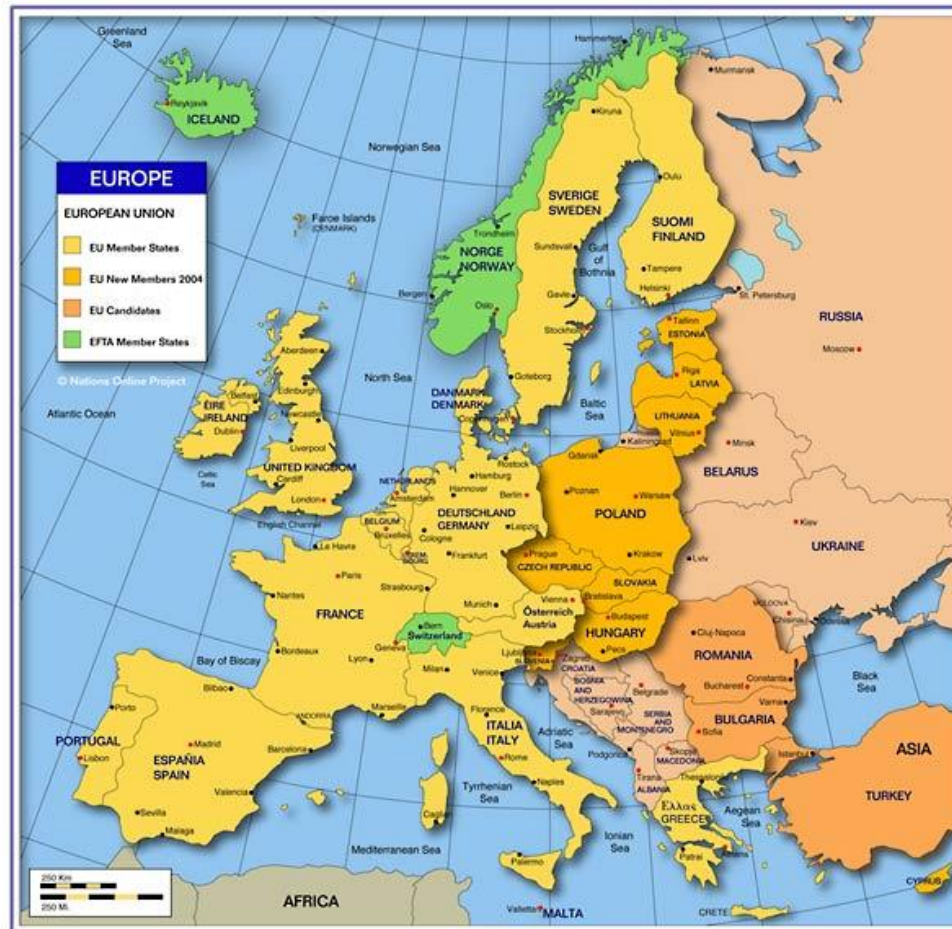
Belgium

Denmark

Radiation

Protection:

Germany



Legal

Representative:

Required by France

European Union: Authorised Representative



Some Ethics Committees (eg Germany, UK) require Non-EEA manufacturers to appoint an Authorised Representative for clinical trials

European Union: Clinical Trial Submissions

- Europe is a unique combination of different cultures and languages. Additionally, there are differences for attaining EC/CA approvals



- D-Target has a specialized team to help sponsor's save time in getting the necessary approvals to start their studies

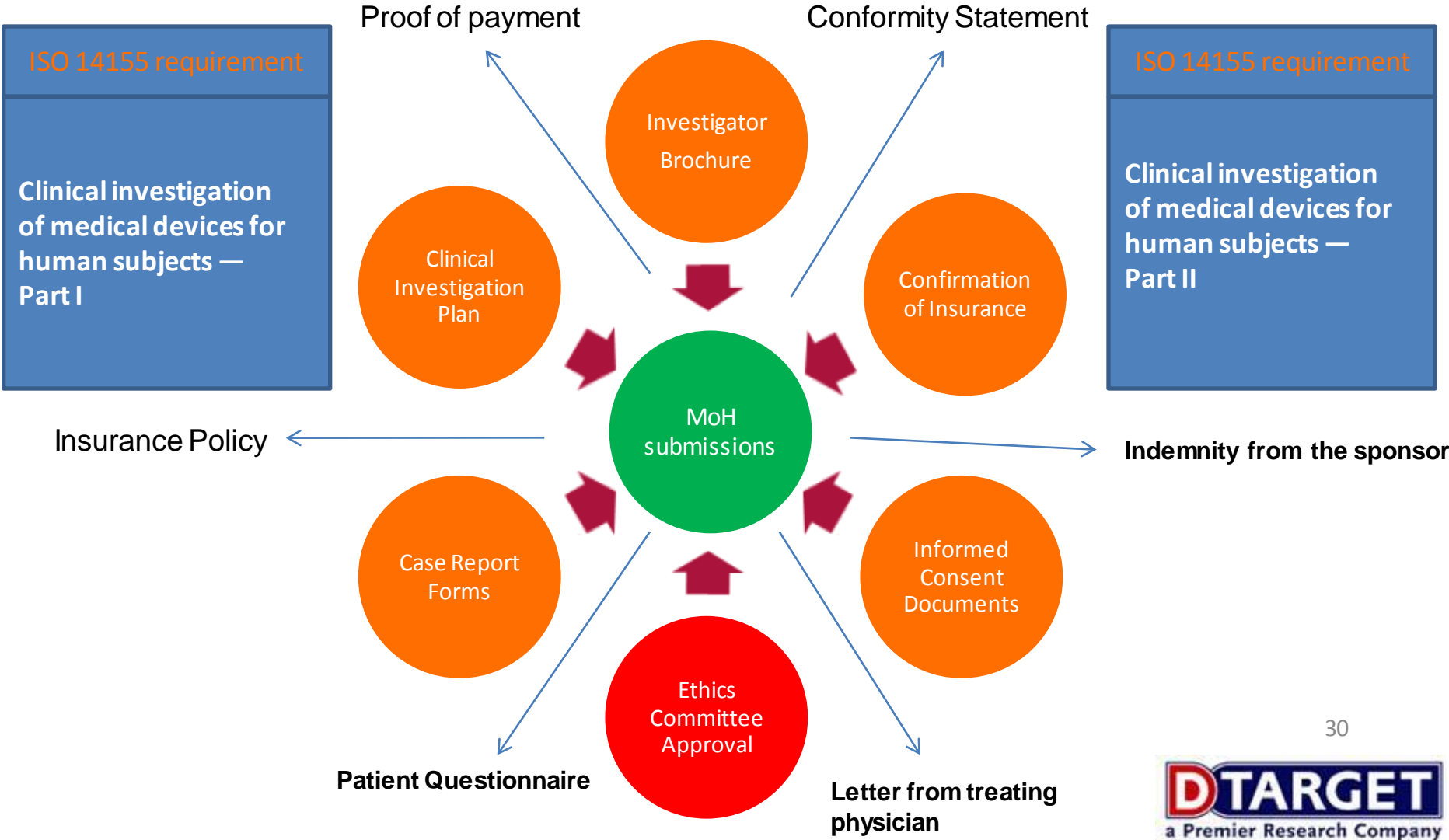
Regulations in Israel



Regulated by the Ministry of Health (MoH); Legislated by national laws

- MoH has two departments:
 1. Device – ISO 14155 for the conduct of clinical trials
 2. Drug - ICH GCP for conduct of clinical trials
- Combination products are usually reviewed by the drug department of the MoH
- Approvals are valid for one year and must be renewed every year
 - Renewal process takes at least 2 months and MUST be initiated 3 months before expiration
 - Failure to conform to this process may lead to:
 - Study recruitment hold
 - Cancellation of study
 - FULL renewed EC submission
- No Data protection submission required (2005-2010)

Device Clinical Trial Submissions in Israel : Ministry of Health requirements



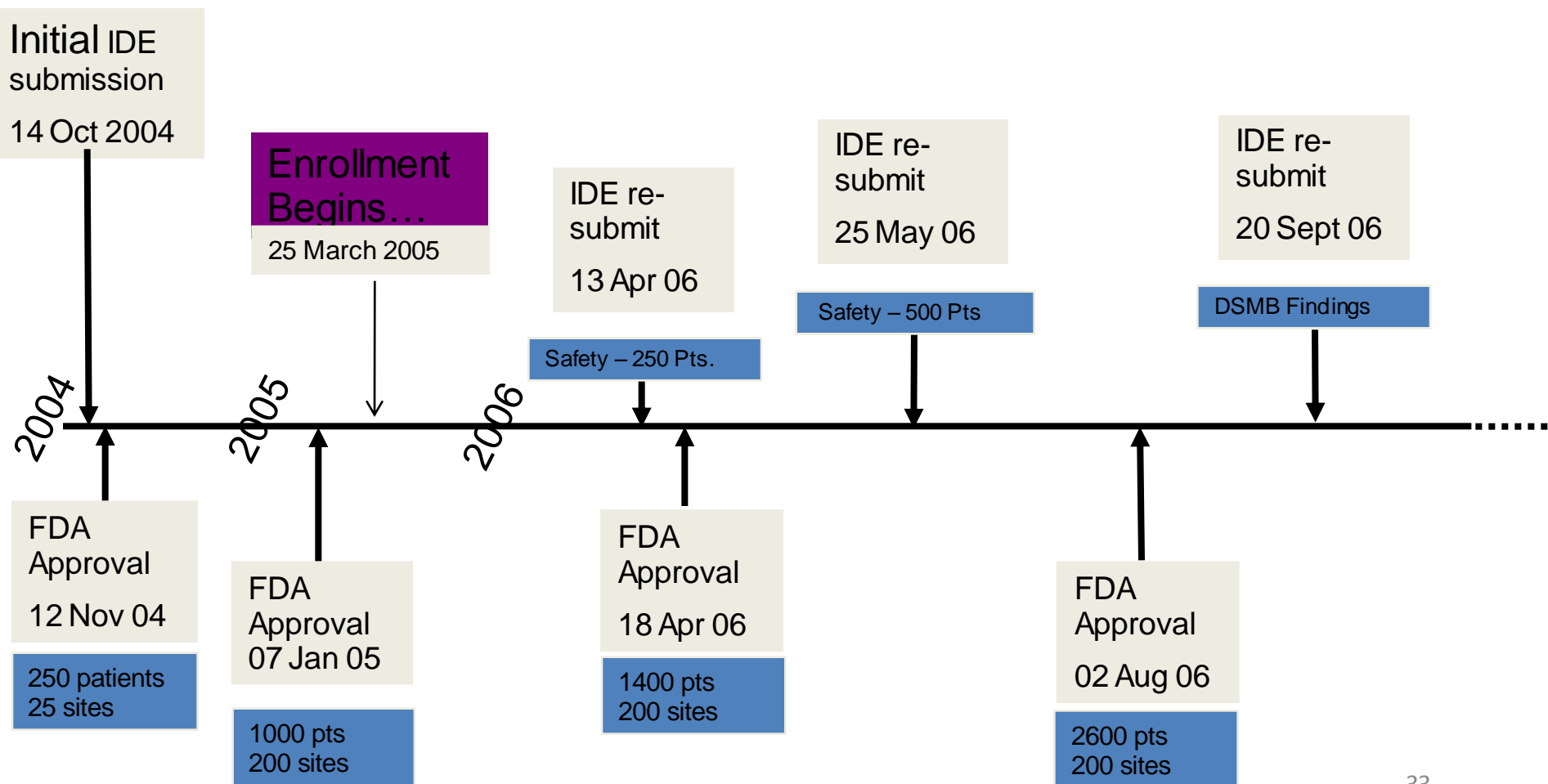
Project Management

- The Project Manager:
 1. The primary contact point for the sponsor
 2. Overseas and coordinates all activities associated with the clinical trial
 3. Produces the status reports throughout the trial
 4. Produces end of study, early termination requirements

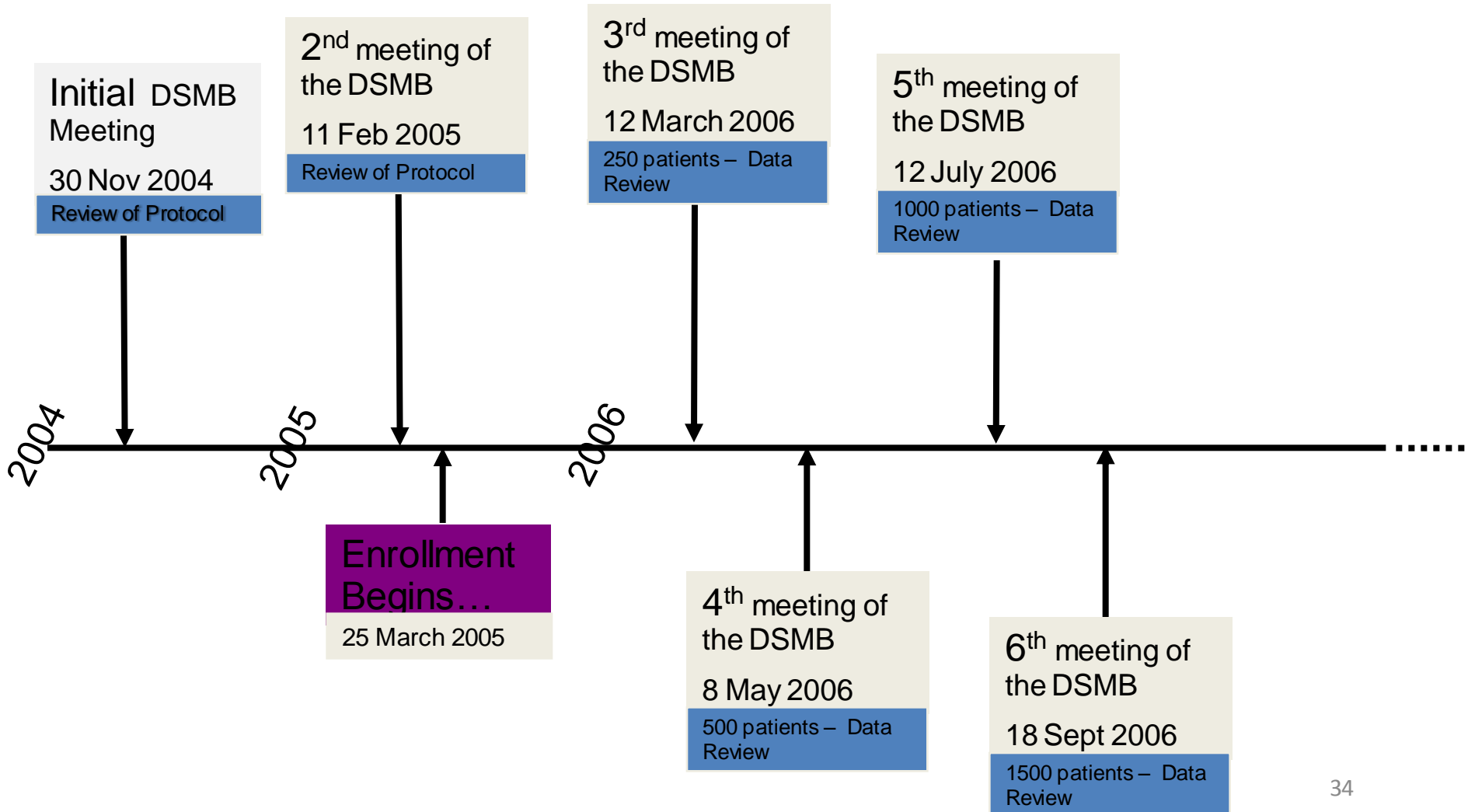
Site Selection

- Site selection is normally an activity of the sponsor although it is discussed with the CRO.
- In this case study, based on their experience, the sponsor identifies good centers and investigators who can provide reasonable patient numbers.

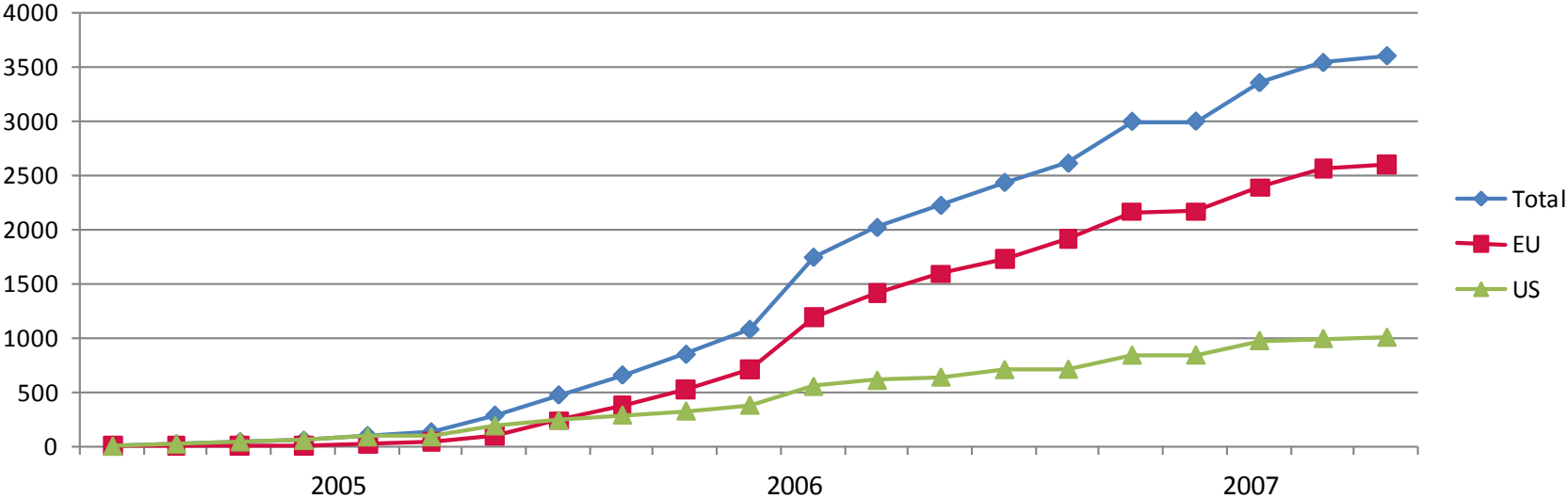
FDA Status Update



DSMB Meetings



Patient Enrollment



Patient Enrollment

- This case study showed that a misjudgement of the ability to enroll sufficient number of patients in the US.
- This resulted in 72% total enrollment in the EU and Israel.
- Conclusion: site selection, patient enrollment can be difficult – proper site assessment, qualification, ability to generate good quality data and experience is necessary.

International Clinical Sites



Monitoring Team – Clinical Research Associates (CRA)

- All CRAs are fluent in English + 1 additional language
- Broad range of monitoring experience
- Broad range of medical experience



Monitoring Visits

- Follow-Up Visits Required:
 - 1, 6, 12 months, and then yearly for 5 years total, for all patients undergoing at least primary randomization
 - Angiography at 13 months for 1,500 stent randomized patients only

Long term studies should consider:

- The interval between monitoring visits
- The need for frequent site contact by telephone ³⁹

Safety Reporting

(2005-21 March 2010)

- Annex X section 2.3.5.: All adverse incidents such as those specified in Article 10 must be fully recorded and notified to the competent authority
- Individual national regulations
- Adverse event = Any untoward medical occurrence in a subject
- Adverse Device effect = Any untoward and unintended response to a medical device
(ISO 14155)

Safety Reporting

(2005- 21 March 2010)

- Safety reporting requirements were not uniform.
- Different EU countries required different reporting requirements (eg. Competent Authorities from CH, DE, NL wanted only Serious Adverse Device Events (SADEs))

Safety Reporting in Israel

Investigator

- **DEATH** - Report death to the EC and director of hospital within 48 hours of knowing it (on a special form – annex 13)
- **Unexpected SAE** (that investigator cannot determine that it was not drug/device related) - Report to the EC and director of hospital within 48 hours of knowing it (on a special form – annex 13)
- **Device Malfunction** - Report to the EC and director of hospital within 48 hours of knowing it, if the malfunction has an effect on the device's efficacy or safety (on a special form – annex 13)
- **SAE Updates from Sponsor** – Report to the EC (only unexpected events that sponsor/investigators did not determine that it was not drug/device related)

Safety Reporting in Israel

Sponsor

- Sponsor must evaluate the safety of the device on an ongoing basis
- Sponsor will notify all involved bodies (investigator, EC and MoH) on every issue that may effect patients' safety or effect the way the study is conducted
- As a rule, the Sponsor will notify the MoH on SADR or SADE that occurred in Israeli centers only:
 - DEATH or life threatening events within 7 days of knowing about it
 - All other SAEs within 15 days of knowing about it
 - IB addenda when included in the Investigators' brochure
 - DSMB conclusions for CIP changes or study stopping within 7 days
 - Study stopping within 7 days

Safety Reporting

Sponsor

***Sponsor does NOT need to report unexpected
SADE that occurred in other countries
(unless lead to a change in the risk/benefit ratio)***

Safety reporting (post 21 March 2010)

M5

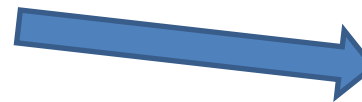
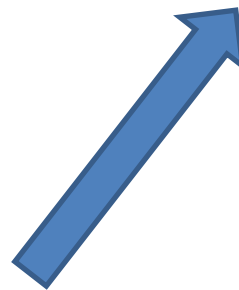
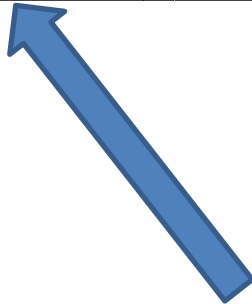
2.3.5. All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed

Safety Reporting: Multi centre trials

(post 21 March 2010)



Serious Adverse Event



Study Close Out

- The FDA, IRB, competent authorities, and ethics committees were informed for the reason for early termination (truncating the study from 5 years to 3 years).
- This reason being the exemplary performance and study outcome.
- All patients sites were informed about the termination of the study.

Study Conclusions

- The drug eluting stent showed superiority over the bare metal stent when used in combination with anticoagulant B.
- This has resulted in a change in clinical regime for patients with ST elevated MI.

Study Conclusions:

Safety reports : Drug and Devices

	Anticoagulant A	Anticoagulant B
Net Adverse Clinical Events	27.60%	25.50%
MACE 1	21.80%	21.90%
MACE 2	16.00%	13.40%
Death	7.70%	5.90%
- cardiac	5.10%	2.90%
- non cardiac	2.80%	3.10%
Stroke	2.00%	1.70%
Major bleeding	10.50%	6.90%
Any stent thrombosis	5.10%	4.50%

	Bare Metal Stent	Drug Eluting Stent
Net Adverse Clinical Events	28.0%	24.50%
MACE 1	24.0%	20.0%
MACE 2	12.9%	13.6%
Death	6.6%	5.6%
- cardiac	3.8%	3.2%
- non cardiac	2.90%	2.4%
Ischemic TVR	17.6%	12.4%
Ischemic TLR	15.1%	9.4%

Project Conclusions

1. Submissions and amendments – understanding the requirements and organisation are key to the process.
2. Site Selection/patient recruitment important to ensure successful completion of clinical trials.
3. Monitoring - enough visits to keep sites motivated, reduce errors, deficiencies.
4. Safety reporting – keep up to date of changes in regulations and any individual CA requirements.

Final Report

- The responsibility of the final report is the sponsor`s.
- The database was locked on 4 November 2010. The final report has been submitted to the FDA.

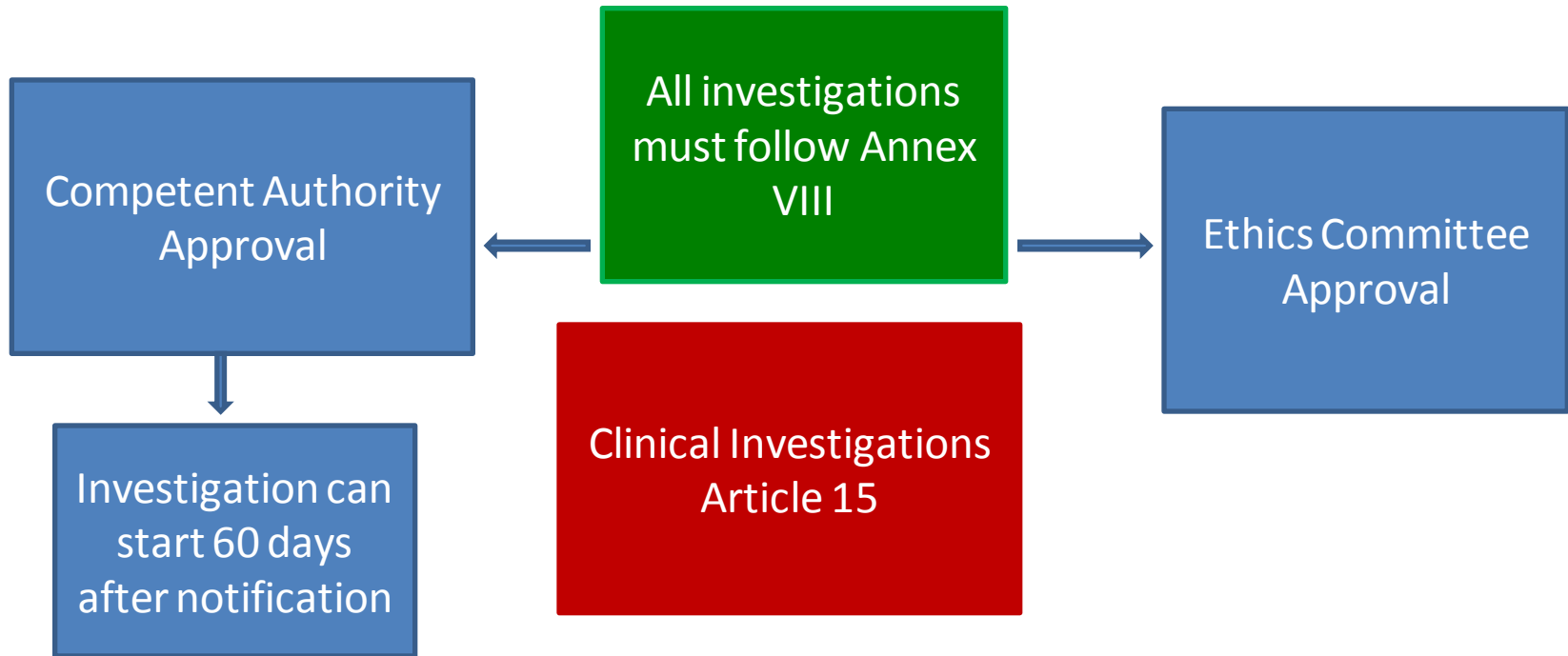
Regulatory Requirement changes

1. Amended Medical Devices Directive
21 March 2010
2. Changes in Germany
3. Changes in Italy
4. ISO 14155 1st Feb 2011
5. Conclusion

Medical Devices Directives: Clinical Data

- Directive: 2007/47/EC became effective as of 21 March 2010.
- To enhance the provisions on clinical evaluation
- Necessary to have clinical data on all medical devices irrespective of classification
- Centralisation of data on clinical investigations in the European Databank: EUDAMED

Medical Devices Directive



Medical Devices Directive:

Annex VIII

- **Section 2.2**

- a. Identification of the device
- b. the clinical investigation plan,
- c. the investigator's brochure,
- d. the confirmation of insurance of subjects,
- e. the documents used to obtain informed consent,
- f. Statements concerning human blood derivatives and animal tissue

- **Medical Devices Directive has always required:**

- (i) the opinion of the ethics committee concerned
- (ii) the name of the medical practitioner, the institution responsible for the investigations,
- (iii) the place, starting date and scheduled duration for the investigations,
- (iv) a statement that the device in question conforms to the essential requirements apart from the aspects covered by the investigations

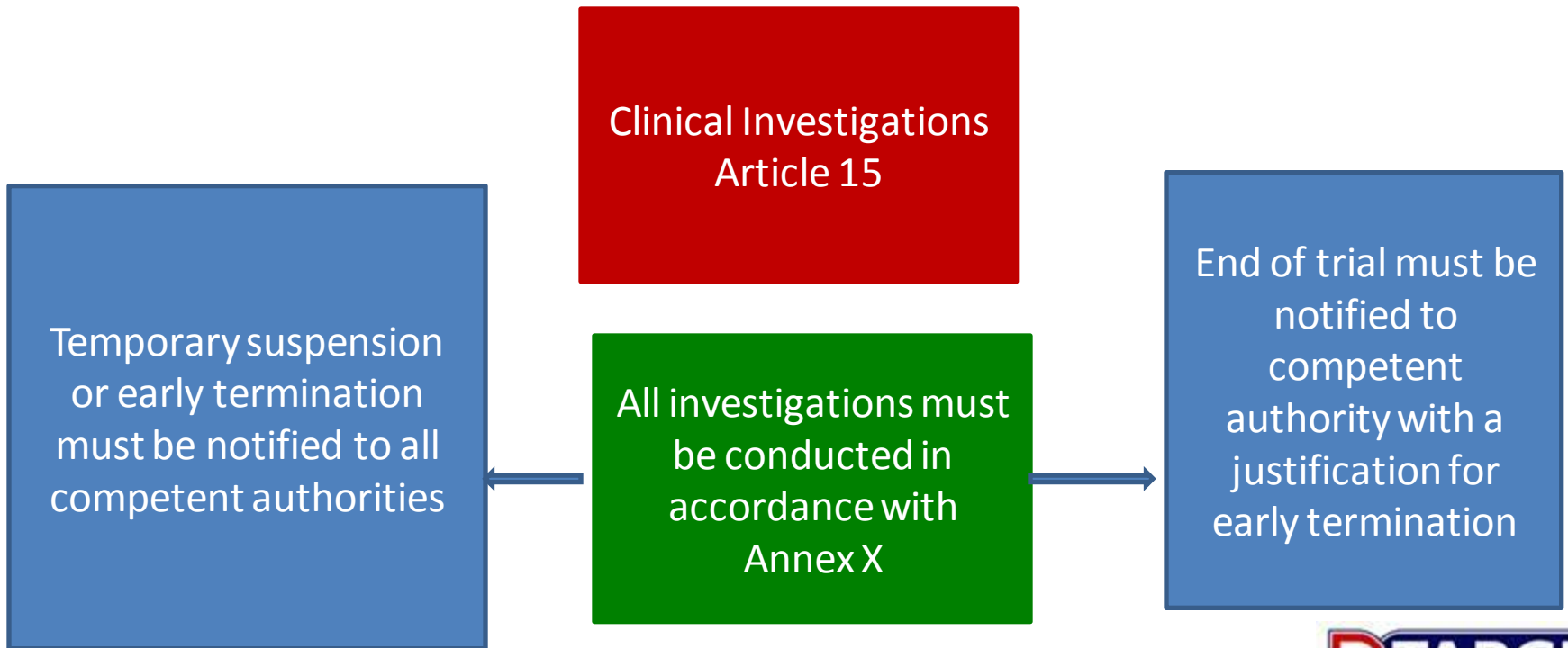
Medical Devices Directive:

Annex VIII

Section 3.2 For devices intended for clinical investigations, the documentation must contain:

- A general description of the product and its intended use,
- Design drawings, methods of manufacture , sterilisation etc.,
- Descriptions /explanations to understand the operation of the product,
- The results of the risk analysis and a list of the standards used
- Use of human blood derivative
-
- Utilisation of tissues of animal origin
- The manufacturer must authorise the assessment, or audit where necessary,
- of the effectiveness of these measures.

Medical Devices Directive



Medical Devices Directive:

Annex X: Clinical Evaluation

- Benefit/Risk ratio must be based on clinical data
- Clinical Data can be:
 - 1.1.1. a critical evaluation of the relevant scientific literature
 - 1.1.2. Or a critical evaluation of the results of all clinical investigations made.
 - 1.1.3. Or a critical evaluation of the combined clinical data provided in 1.1.1 and 1.1.2.
- 1.1a In the case of implantable devices and devices in Class III clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.
- 1.1b The clinical evaluation and its outcome shall be documented. This documentation shall be included and/or fully referenced in the technical documentation of the device.
- 1.1c The clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance.
- 1.1d If clinical data is not deemed appropriate adequate justification must be provided.

Medical Devices Directive:

Annex X: Clinical Evaluation

2.2. Ethical considerations

- ► **M5 Clinical investigations must be carried out in accordance with the Helsinki Declaration** adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly. ◀ It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.

Medical Devices Directive:

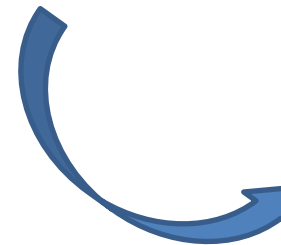
Annex X : Clinical Evaluation

Section 1.1c

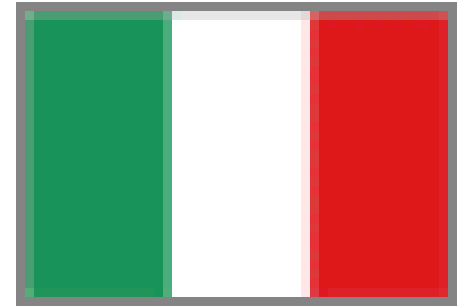
The clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance. Where post-market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.

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Germany



Italy



Requirement: devices must be provided for free for clinical investigation

No longer the case for CE marked devices

Different requirements for Public and Private hospitals

In the past private hospitals had a longer waiting time – NO LONGER THE CASE

A notification letter must be sent to the CA

Clinical Investigations

- Standards are required to ensure:
 - protection of human subjects in the investigation
 - establishing and ensuring scientific conduct of the investigation
 - establish a code of conduct to be followed in clinical investigations

ISO 14155:

Clinical investigations of medical devices for human subjects – Good Clinical Practise

" This international Standard addresses good clinical practise for the design, conduct, recording, and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes. "

Released 1st February 2011

ISO 14155: 2011

ISO 14155:2003
Part 1 (General
Requirements)

ISO 14155:2003
Part 2 (CIP)



ISO 14155: 2011

A	A	A	A	A	A	A
n	n	n	n	n	n	n
e	e	e	e	e	e	e
x	x	x	x	x	x	x
A	B	C	D	E	F	

Annex A = CIP

Annex B = Investigator Brochure

Annex C = Case Report Forms (CRFs)

Annex D = Clinical Investigation report

Annex E = Essential clinical investigation docs

Annex F = Adverse event categorisation

ISO 14155 : 2011 published on 1st Feb 2011

Not harmonised yet

Substantial Amendments

- Definitions: point of enrollment, safety reporting
- Sponsor Responsibilities
- Informed consent for vulnerable subjects
- Ethics Committees
- Study Monitoring
- Electronic Data Management
- Risk Management

Presumption of Conformity

- MDD 93/42/EEC (Art 5) and AIMDD 90/385/EEC (Art 5) :
- Compliance with EU harmonized standards carries a presumption of conformity with the medical device directives Essential Requirements

Which Standards Should be Followed?

- **Which regulations to use for medical device studies?**
- **Most important question** : “Where do we want to or where do we intend to register the product?”

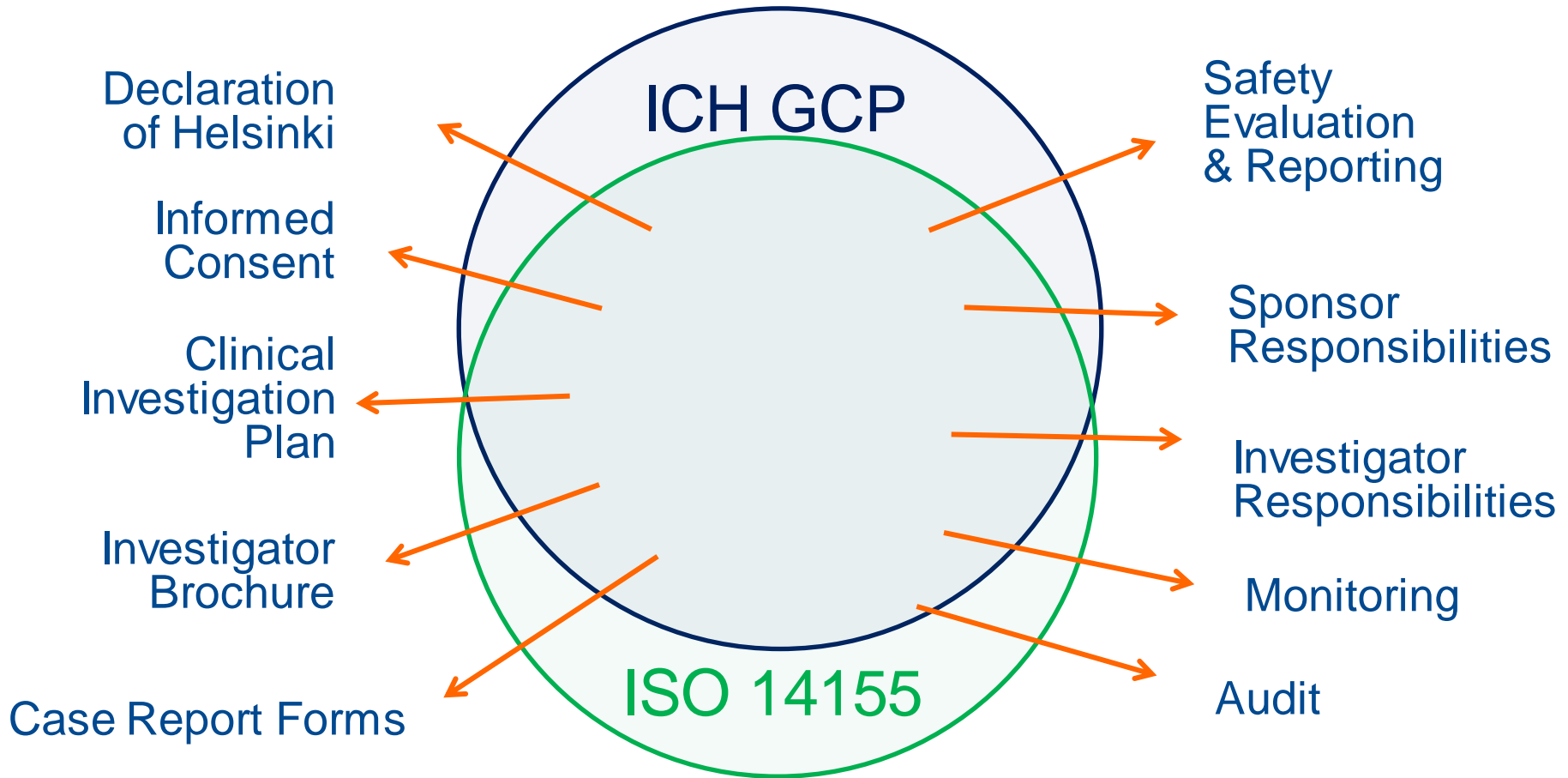
Europe	USA	Japan
<ul style="list-style-type: none">• National regulations• ISO 14155: 2011	<ul style="list-style-type: none">• 21 CFR parts 812, 50, 56 and 814• ICH-GCP	<ul style="list-style-type: none">• National law• ICH-GCP

ICH E6:

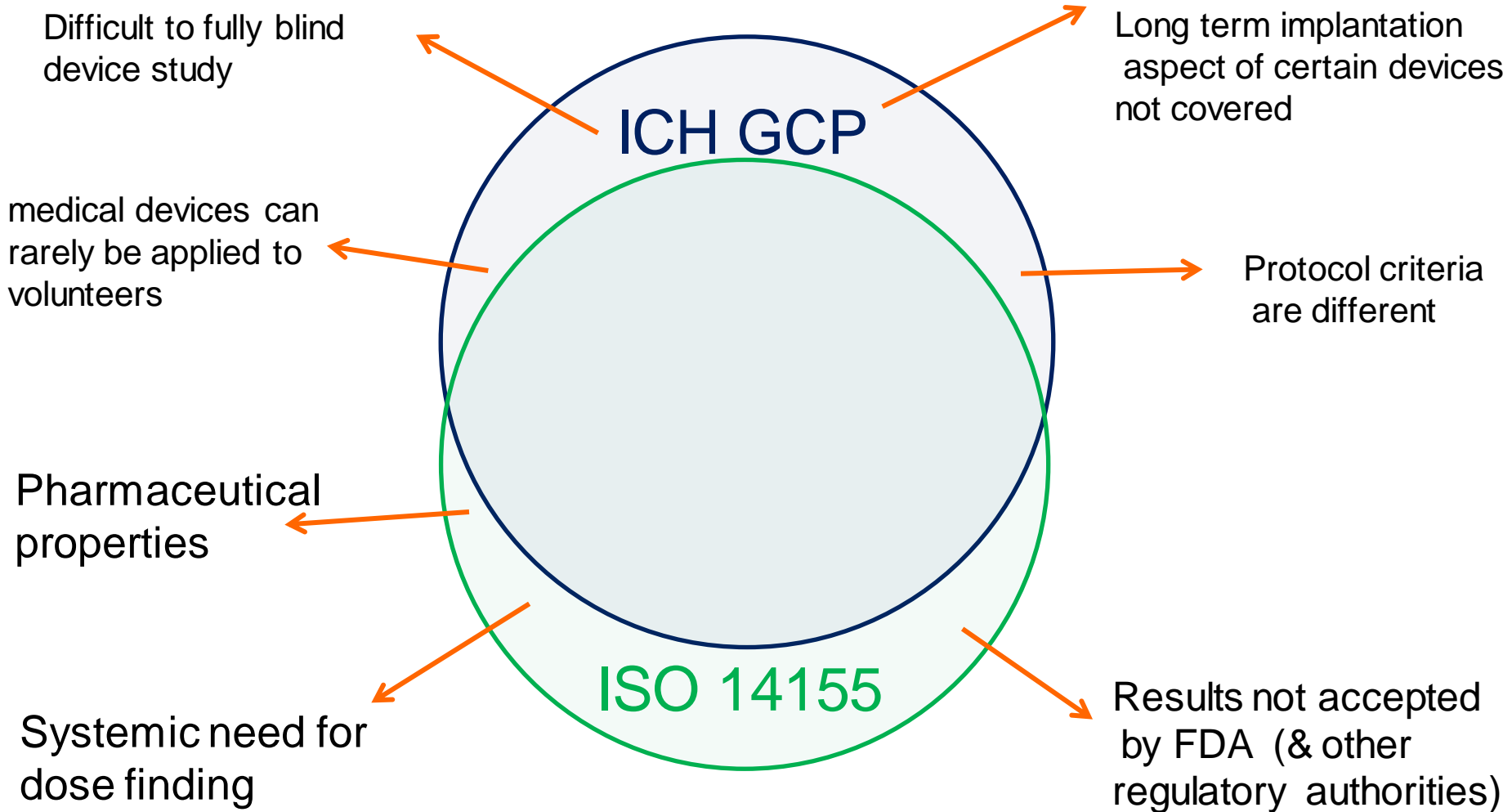
International Conference on Harmonisation Guideline for Good Clinical Practice

" Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. "

ISO 14155 v GCP



ISO 14155 v GCP



Conclusion

1. Changes in the Medical Devices Directive place greater emphasis on Clinical Data
2. Requirements for clinical trial submissions have not changed significantly.
3. Members States: Germany and Italy have the largest changes.
4. Safety reporting requires:
 - a. reporting of all serious adverse events
 - b. Informing all Member States that are involved in a clinical trial
5. Increased emphasis on clinical data through the Post Market phase.

Thank you for your attention

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