INSIDE INNOVATION

Corso di Biotecnologie applicate
A.A. 2024-2025

Milena Sinigaglia,
Alifax R&D
Trieste, 28th March 2025

1. Who we are?
2. What is an *In Vitro Diagnostic* device
3. Academy vs Company
4. Project management
5. In Vitro Diagnostic device development

After graduation?

After graduation?

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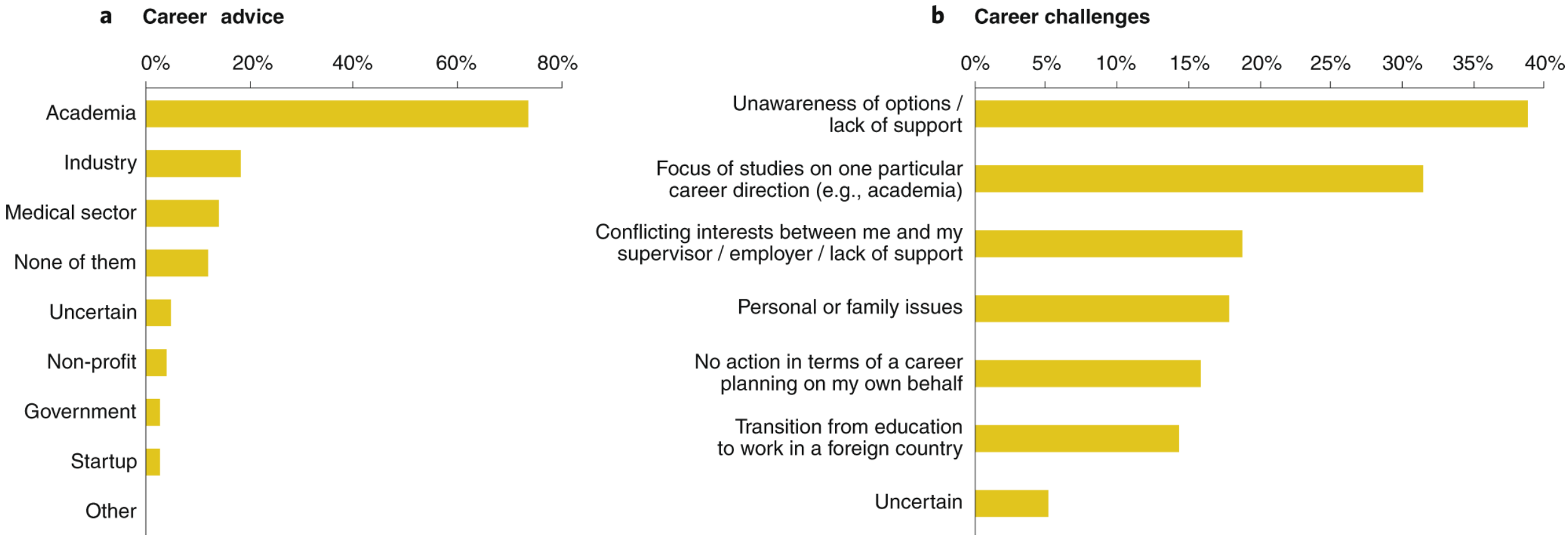
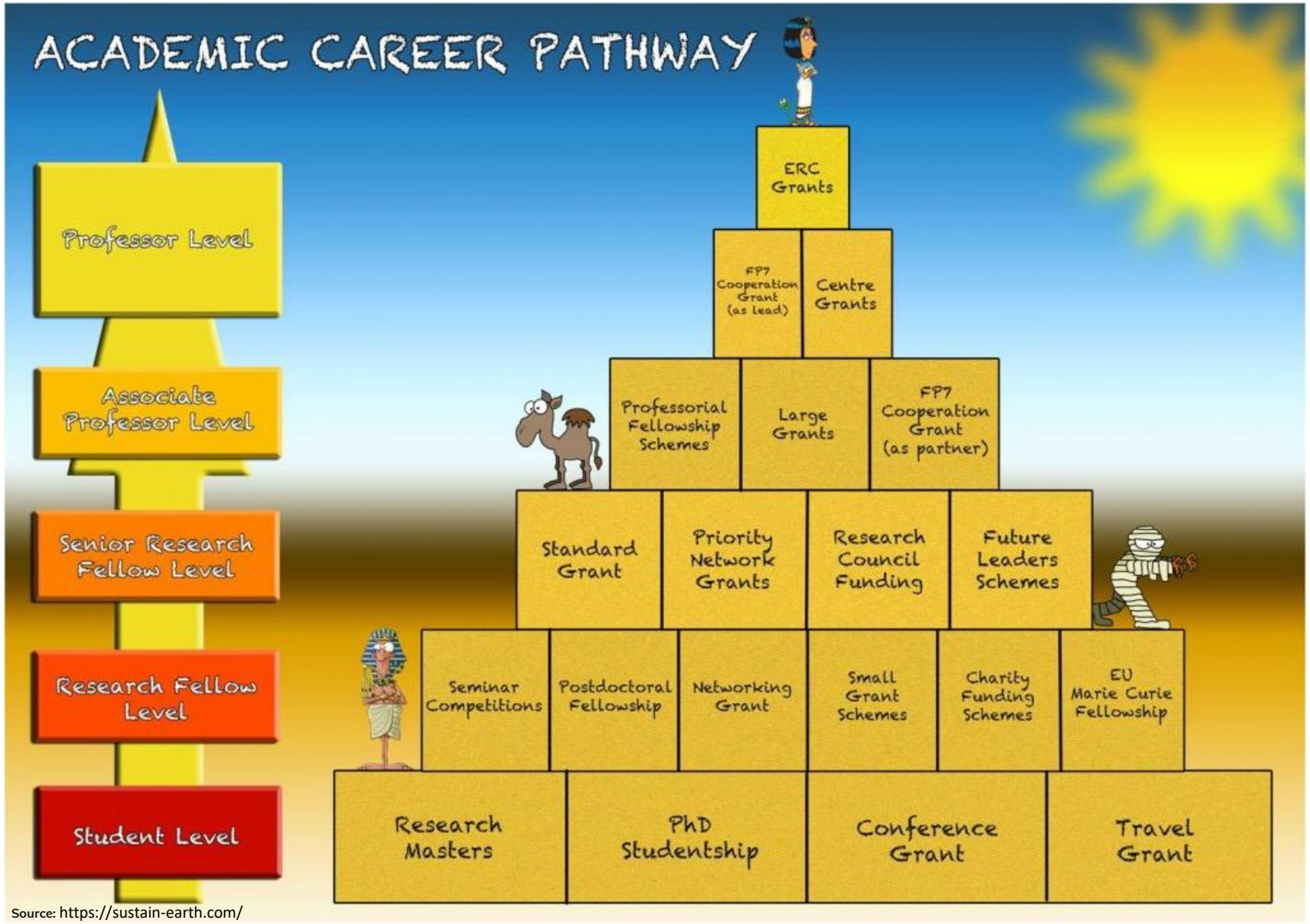


Survey of 300 graduate and postgraduate students in the United States and Europe.
a. Students received the most career advice about academic careers. b. A large proportion of students felt a lack of support and awareness of career options blunted their ability to reach their ideal careers.

Academic career



Source: https://sustain-earth.com/

Industrial career

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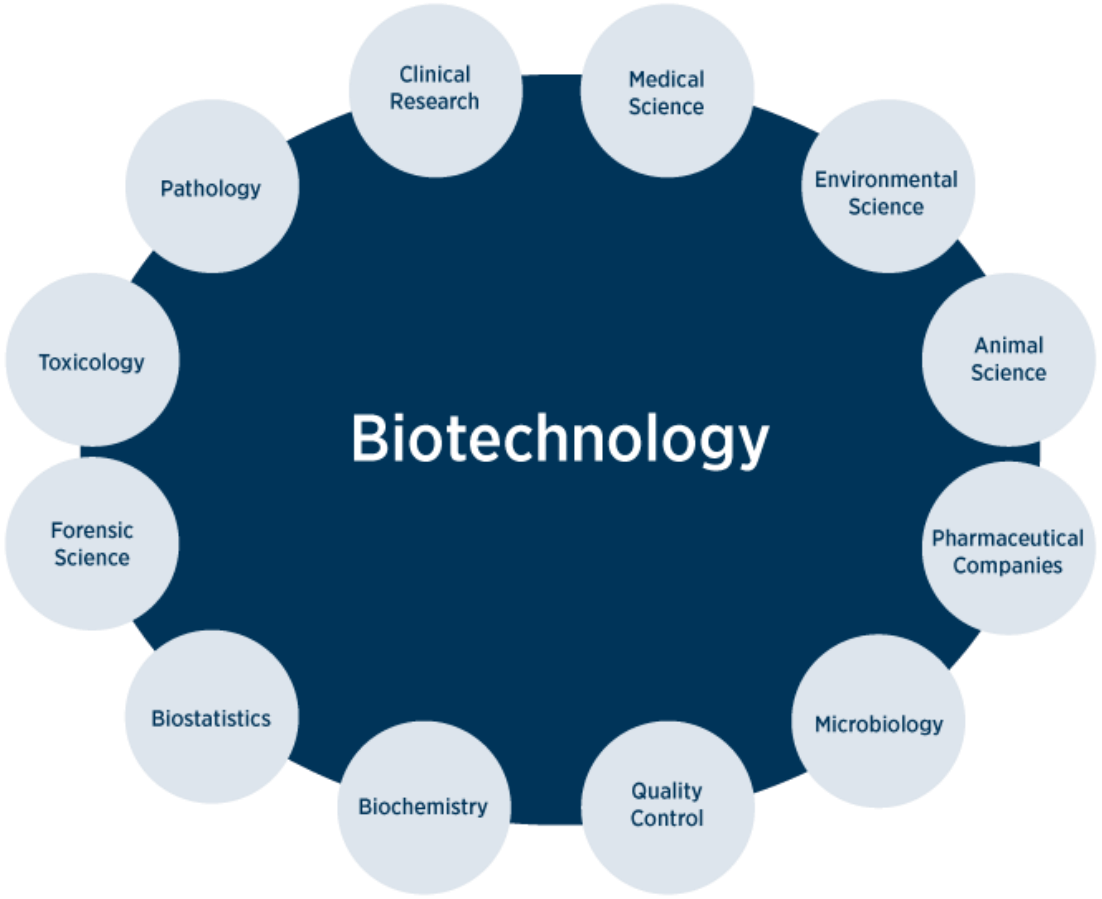

Source: www.careerguide.com/

Marketing

R&D

Production

Quality control

Scientific technical support

Administration

Product Specialist

Manager

Sells

Technician

Basic research as a road toward a better life

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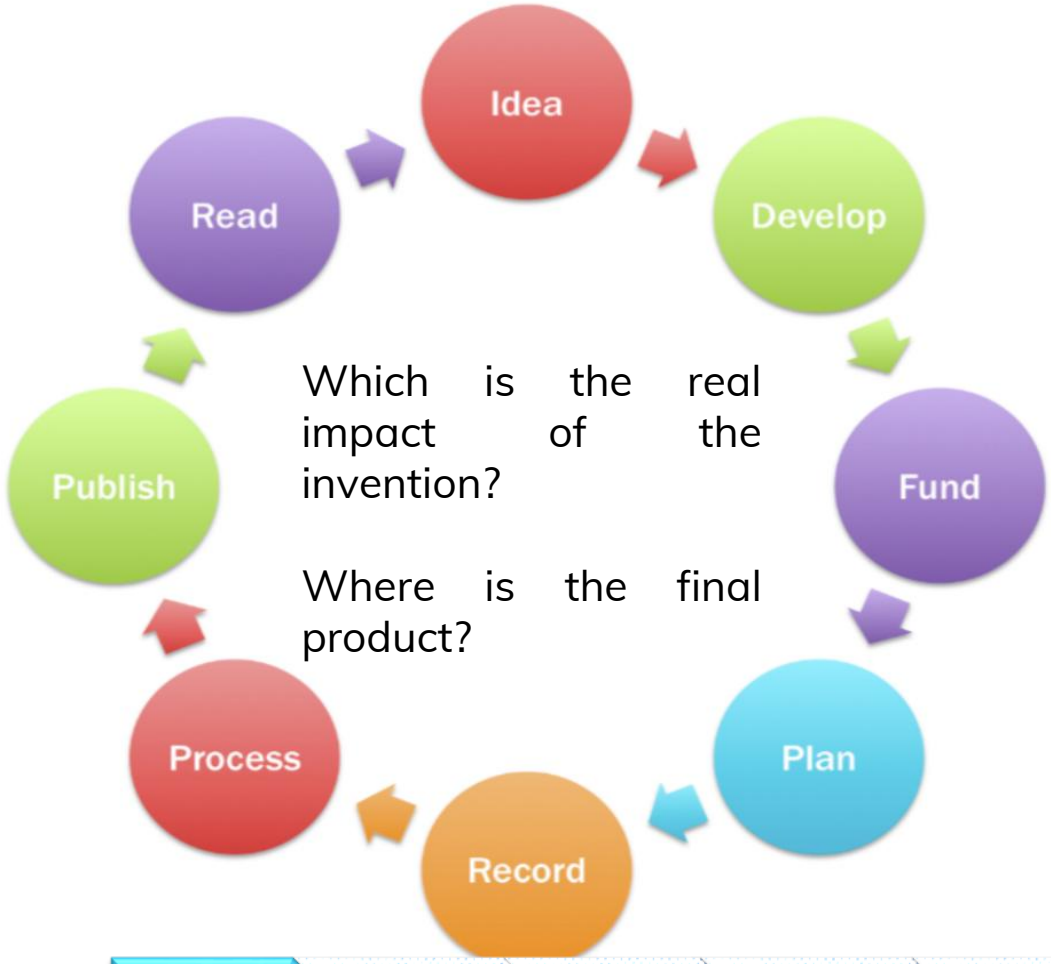
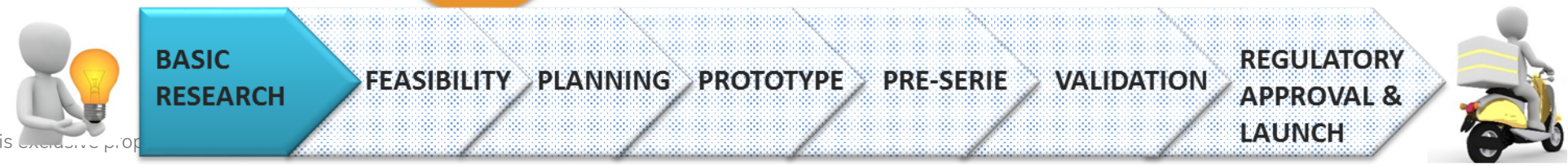


The final aim of basic research is to increase knowledge to improve the quality of life.

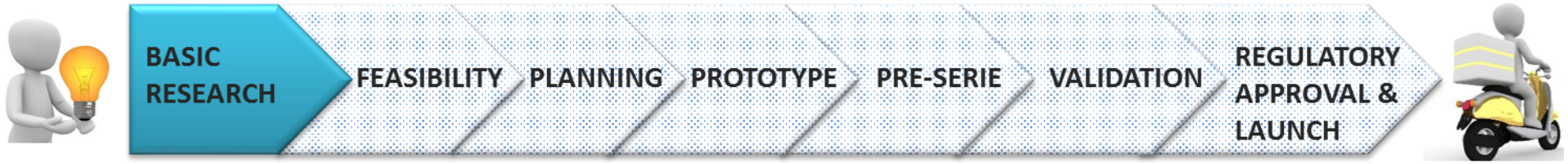
Sometimes useful R&D ideas can not be translated into a product due to feasibility issue



Basic research: different perspectives academia vs industry

- Idea
- Protocol
- Sample
- Disease
- Collaboration
- Impact Factor

- User needs
- Competitor / Patent
- Quality / Costs
- Prototype production, verification, validation
- Time to market



Basic vs Applied Research

Research

- *noun*: the systematic investigation into and study of materials and sources in order to establish facts and research new conclusions.
- *verb*: investigate systematically

Industrial research

The planned research or critical investigation aims at the acquisition of new knowledge and skills for developing new products, processes or services or for bringing about a significant improvement in existing products, processes or services. (source 'European Union')

Basic vs Applied Research

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Basic Research

- To accumulate information, extending the base of knowledge ina discipline - why?
- Pure science (i.e. Bech scientist/ natural science)
- Identify functional relationships
- May not have immediate relevance
- Critical to the survival of applied research

Applied Research

- To find immediate solution to an existing problem-what is the goal?
- Clinical science (i.e. Practice settings)
- Development of new products, processes or services or for bringing about a significant improvement in existing products, processes or services
- Aimed to solve problems
- Based on basic research

Basic vs Applied Research

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Academic Research

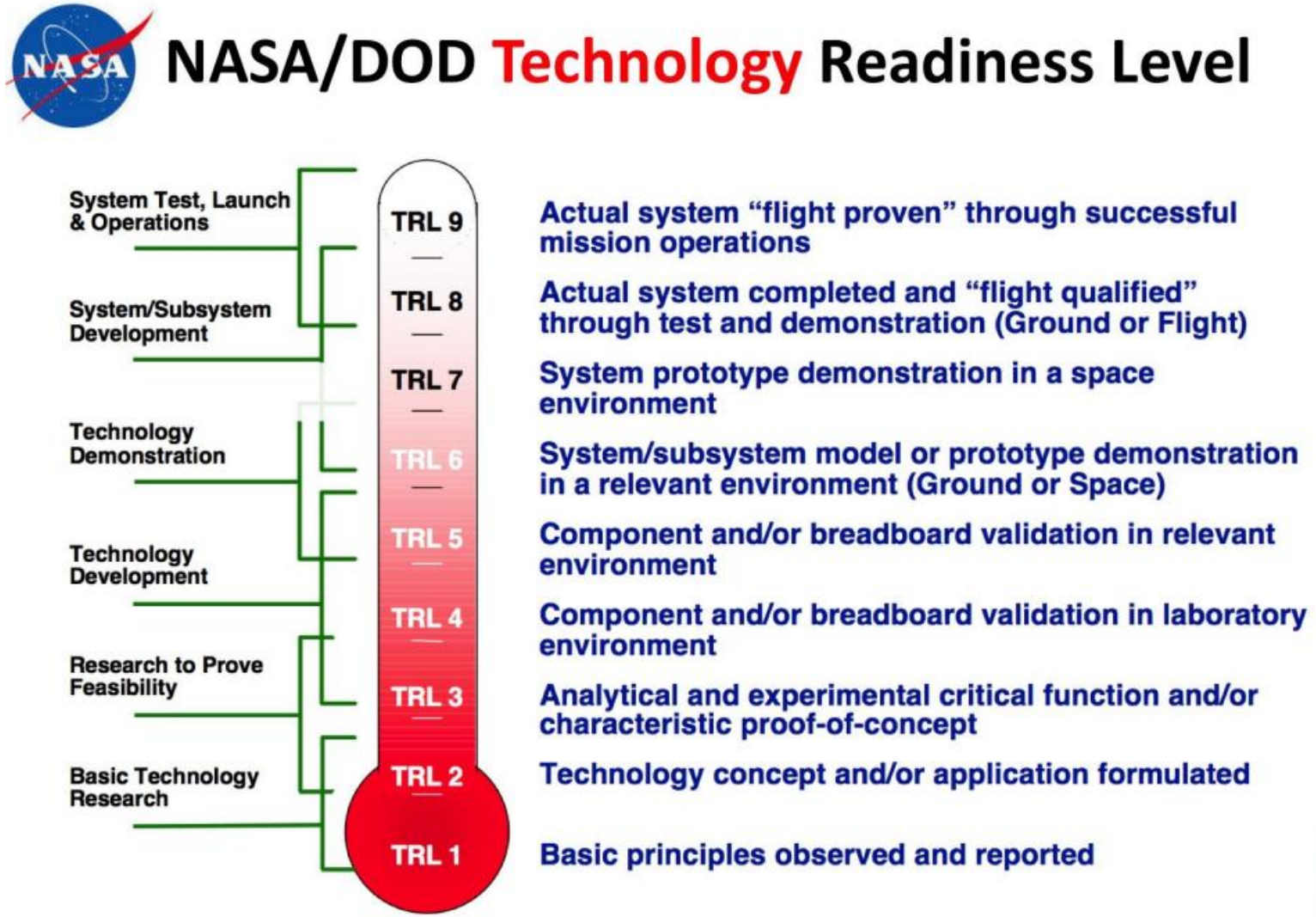
Both positive and negative outcomes are equally valid and important contributions to the body of knowledge that the world shares

Industrial research
industrial research success is new knowledge that leads to new products, processes or services. Due diligence needed to invest only in feasible projects.

Industrial research is similar to, but distinct from, academic research. Both fields share the **same rigour**, although their **goals** are **different**. Within the academic world success can be defined as discovering new knowledge. There is a subtle but important difference which affects the type of research and hence work that industrial research teams undertake to reach the market and improve disease management.

Technology Readiness Level

NASA developed it during 1974 in respect of planning the Jupiter Orbiter design team. The original definition of TRL involved seven levels of development stages, but the current one, which has been adopted by NASA and European Union, now has nine levels.



Source https://www.researchgate.net/

Technology Readiness Level

TRL 0: **Idea**. Unproven concept, no testing has been performed.

TRL 1: **Basic research.** Principles postulated and observed but no experimental proof available.

TRL 2: **Technology formulation**. Concept and application have been formulated.

TRL 3: **Applied research**. First laboratory tests completed; proof of concept.

TRL 4: **Small scale prototype** built in a laboratory environment ("ugly" prototype).

TRL 5: **Large scale prototype** tested in intended environment.

TRL 6: **Prototype system** tested in intended environment close to expected performance.

TRL 7: **Demonstration system** operating in operational environment at pre-commercial scale.

TRL 8: **First of a kind commercial system**. Manufacturing issues solved.

TRL 9: **Full commercial application**, technology available for consumers.

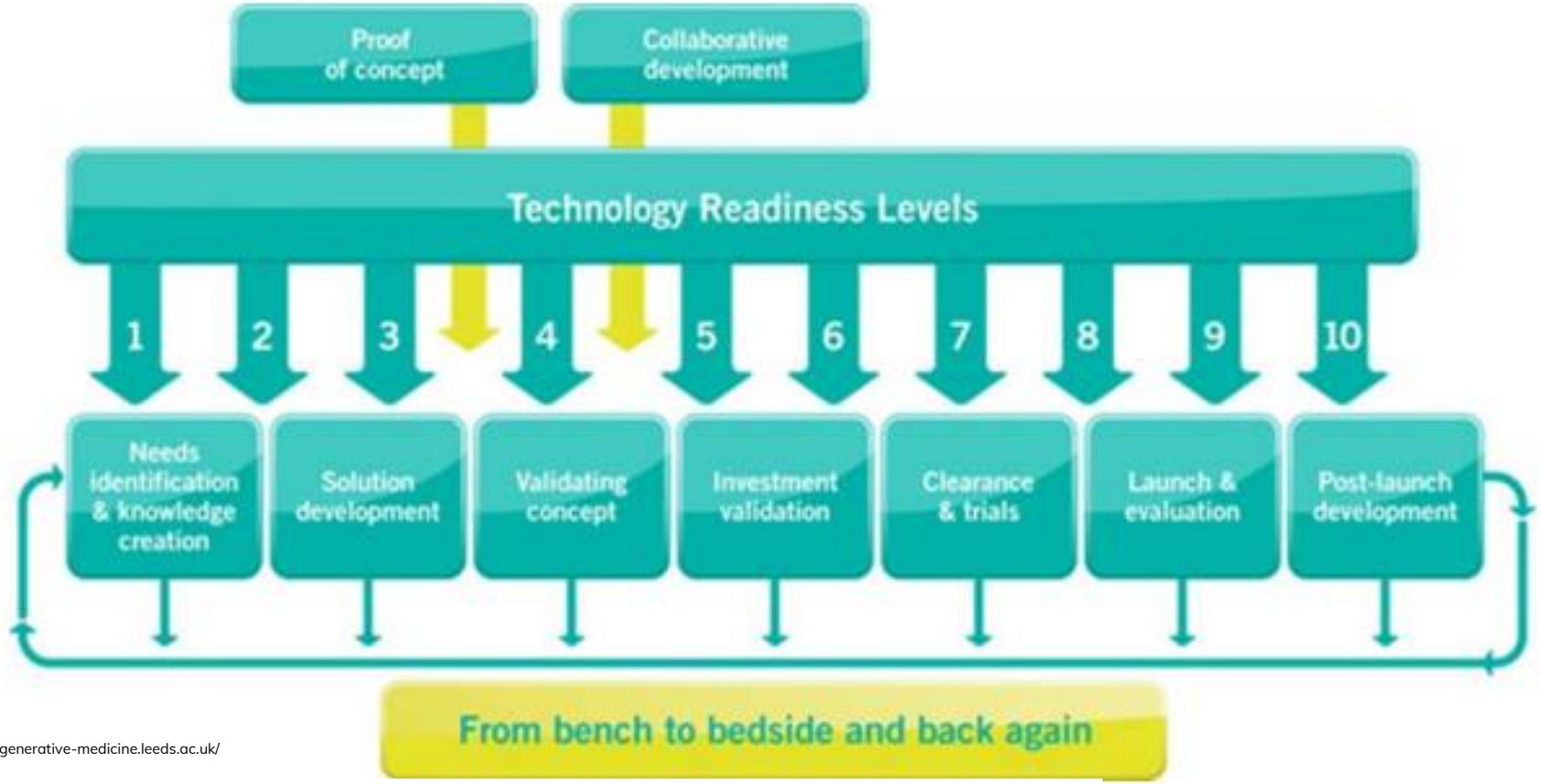
Source: European Commission

TRL evaluation applied to several applications

Technology Readiness Level

TRL 1	TRL 2	TRL 3	TRL 4	TRL 5	TRL 6	TRL 7	TRL 8	TRL 9	TRL 10
Basic Research	Preclinical Research / Proof of Concept	Manufacturing Validation / Late Preclinical	Clinical Phase	Regulatory Clearance & market preparation	Post-Launch				

Example of Technology Readiness Levels (TRL) using in medical device development



Source: https://regenerative-medicine.leeds.ac.uk/

Technology Readiness Level

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Technology Readiness Level (TRL)						
1-2	3	4	5-6	7-8	9	10
Clinical need defined & knowledge created	Solution Generation	Investment Validation	Development & Validation	Clearance & Clinical	Outputs / Outcomes	Post Launch Market Support
Define clinical need/relevance Develop/refine solution IP	Generation of Prototypes IP Preliminary Value Proposition Risk Assessment	Market Research FTO searches Pilot Studies	Design Control Regulatory Capability	Market support data Supply Chain Reimbursement considerations Capability Clinical	Regulatory Approval Closure & Evaluation Metrics Feedback / Launch SOP	Product Support data White Paper Product Recall Support

T1 T2

IP: Intellectual Property
FTO: Freedom to Operate (commercially 'safe' for you to make / sell your product)
SOP: Standard Operating Procedures

First gap (T1): "…translating ideas from basic and clinical research into the development of new products and approaches to diagnosis/prognosis/treatment of disease and illness"

Second gap (T2): "…implementing those new products and approaches into clinical practice" – ie disconnect between the development and the implementation of new interventions"

Source:A review of UK health research funding. London: HM Treasury, 2006/

Basic research: different perspectives academia vs industry

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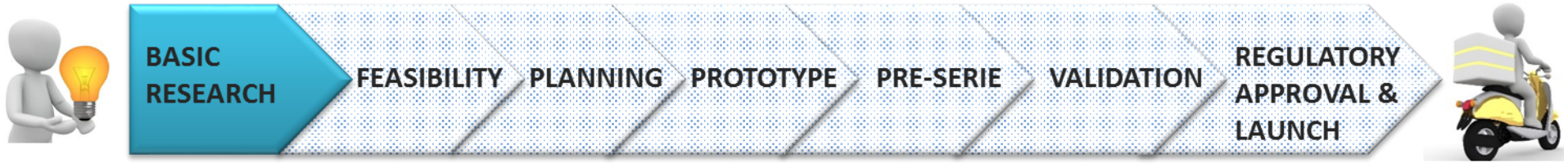
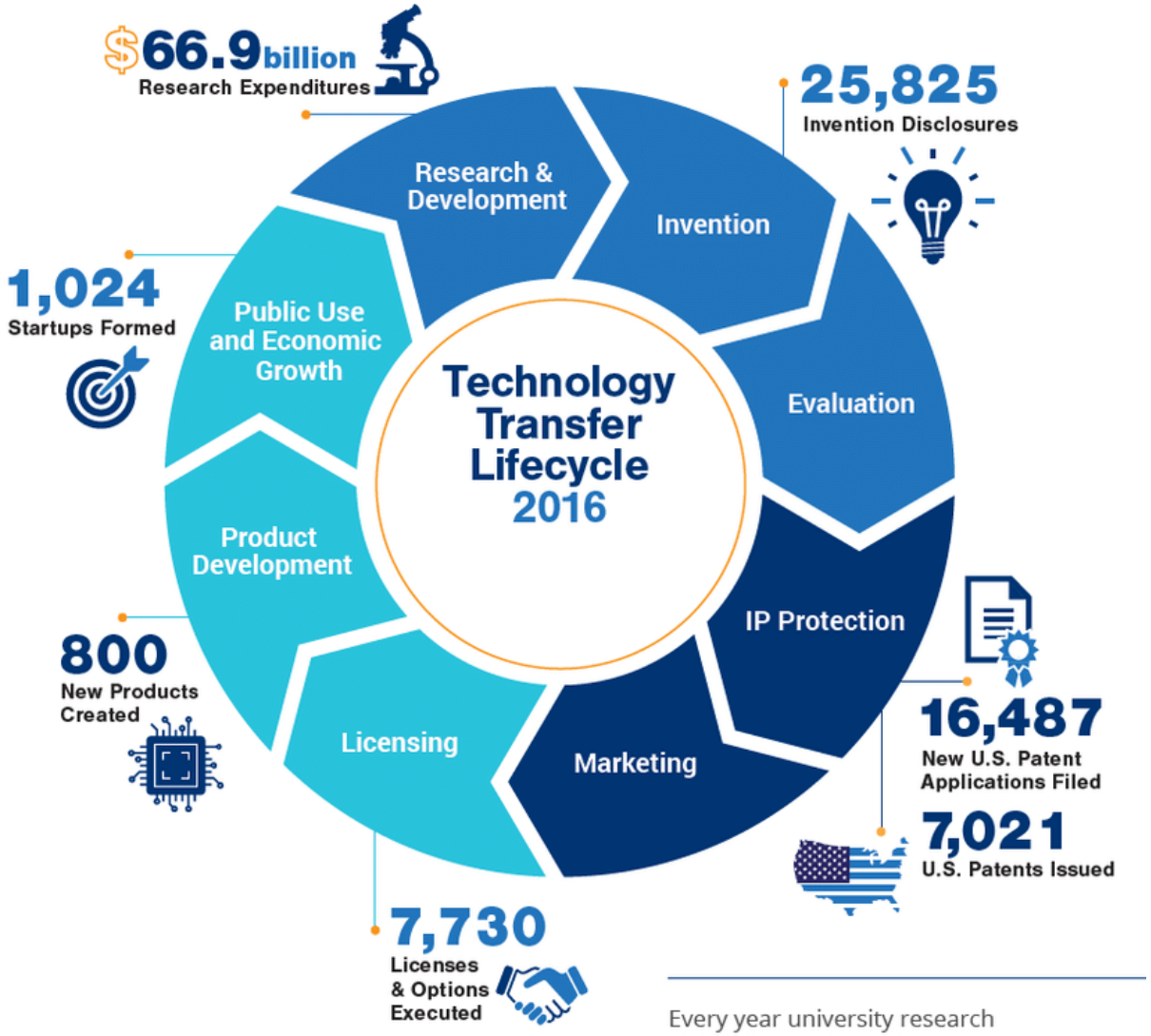


Technology Transfer

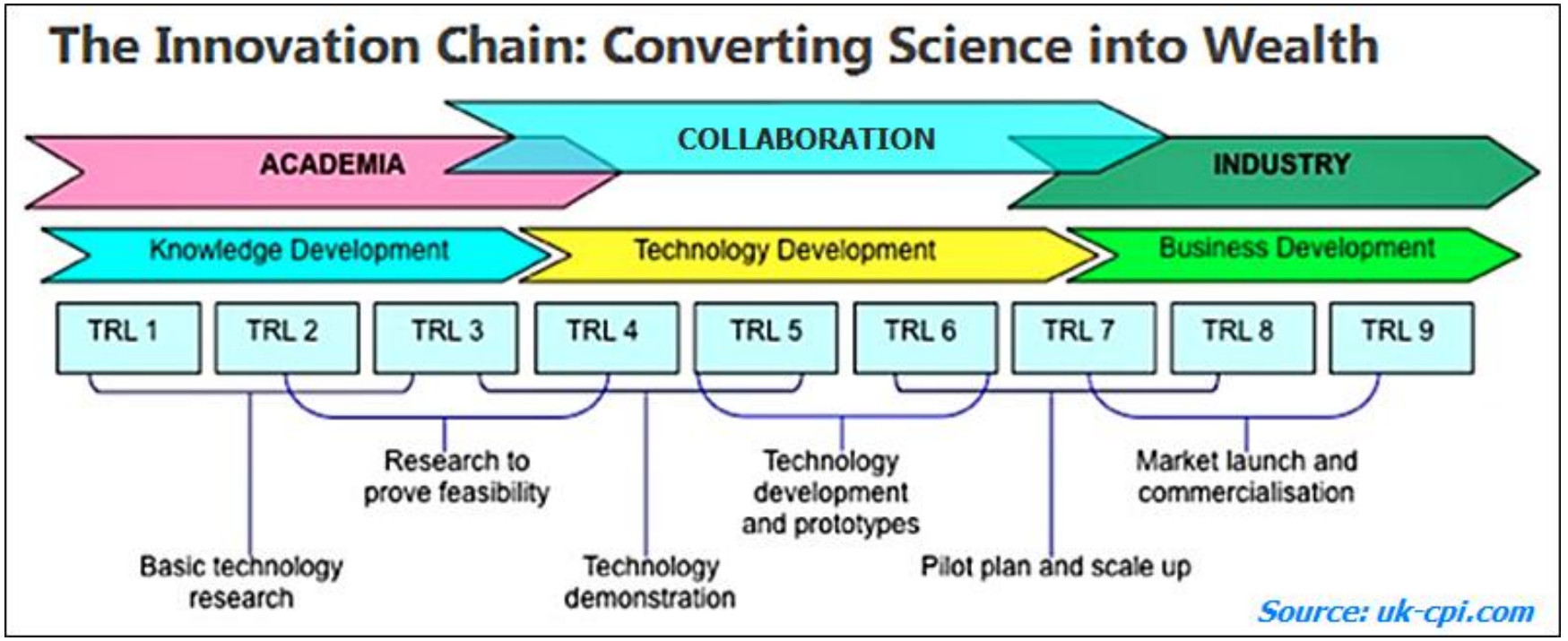


Every year university research yields discoveries with commercial potential.

Sourcehttps://www.researchgate.net/

Technology Transfer

Technology transfer (TT) refers to the process of conveying results stemming from scientific and technological research to the market place and to wider society, along with associated skills and procedures, and is as such an intrinsic part of the technological innovation process.



Technology Transfer

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Company

- Idea
- Protocol
- Experiments on clinical samples
- Case studies
- Patent (?)

End user

- Scientific validity
- Feasibility
- State of the art
- Development/Production costs
- Time to market

Patient

- Clinical practice feasibility
- Diagnostic accuracy/reliability
- Time to Result
- Cost
- Risk/benefit

Example of Tech Transfer proposal

4 miRNA x diagnosis of Venous Thrombosis

CLINICAL NEED

Venous thrombosis (VT) is a complex condition and chronic disease with a highly heritable genetic component in people with acquired genetic disorders of hypercoagulation and it is also associated to several conditions such as hospitalization, immobility, trauma, pregnancy and cancer. Common associated life-threatening disorders are Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), which presents a recurrence risk in 30% of all patients within the first 10 years post first event.

Current diagnostic methods both of DVT and PE are based in imaging techniques (MRI, PET, ultrasound, X-ray) and in-vitro procedures (D-dimer blood test) which cannot be used for predictive use.

INNOVATIVE ASPECTS

The identification of these 4 validated innovative plasma miRNAs biomarkers will allow:

- The development of a non-invasive diagnostic and prognostic kit.
- The prediction for the risk of venous thrombosis event based in MicroRNAs.
- The diagnosis/prognosis of those people who would not be detected to develop thrombosis through conventional risk factors.
- To assess the risk of recurrence of thrombosis in patients who have already had it.

MARKET SIZE

VT incidence is estimated at 1 to 2 per 1000 person-years, of which 30% will experience recurrence within 10 years after the first event.

The current market for DVT and PE are focussed in the diagnostic and treatment phases. Therefore, the current invention can address a % of these markets, reducing the cost associated to recurrent events. For instance, the DVT treatment market is expected to witness market growth at a rate of 9.5% in the forecast period of 2021 to 2028.

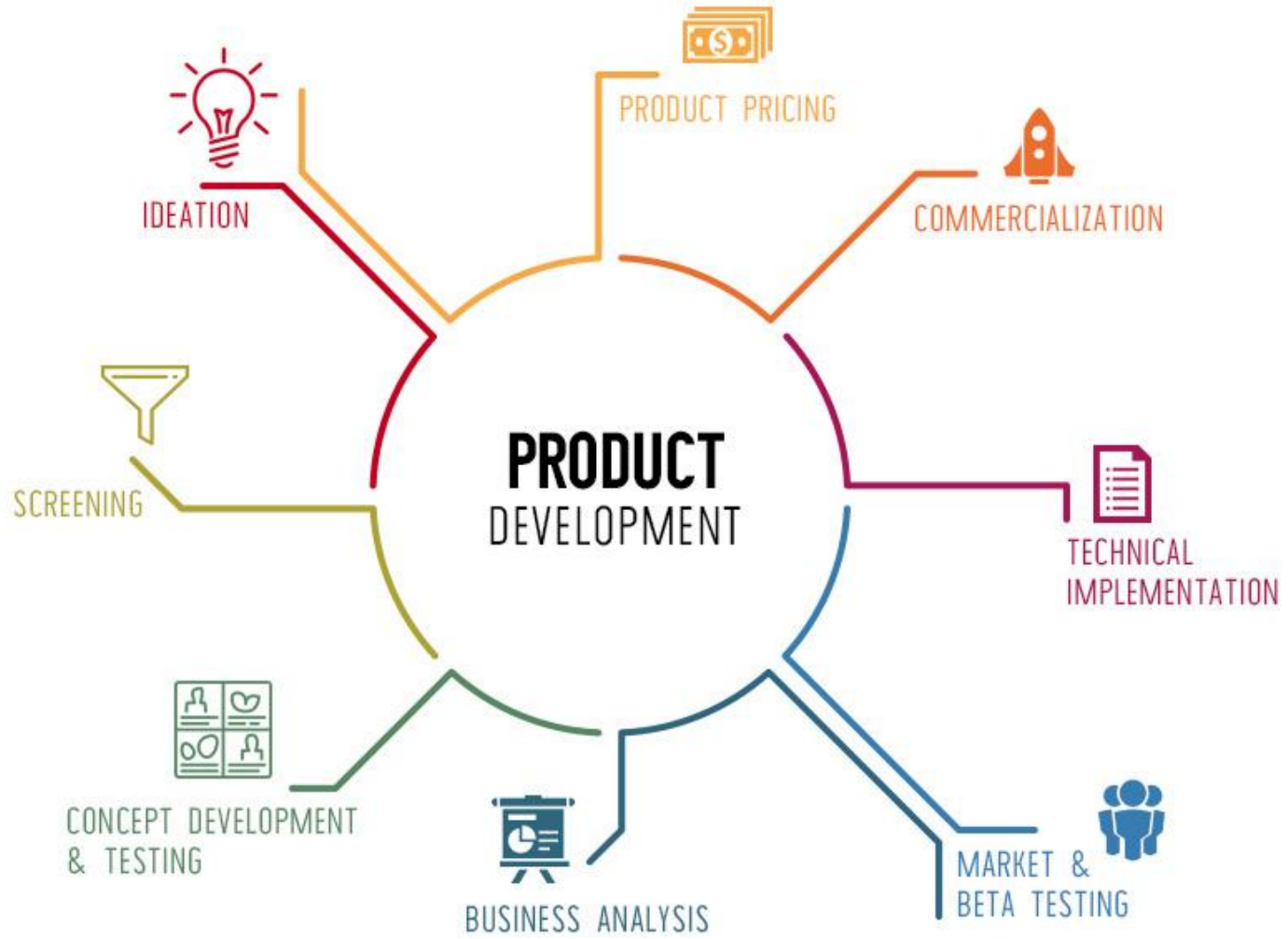
STAGE OF DEVELOPMENT

The current invention has been demonstrated in a research study with the largest sample to have been examined. The 4 miRNAs biomarkers have been validated to be differentially expressed in patients with VT and its potential as predictors of VT discussed. Next steps are to develop a prototype of the diagnostic kit and validate it.

INTELLECTUAL PROPERTY

PCT patent application: PCT/EP2021/055174 (2/3/2021). Priority date: 2/3/2020. The patent protects the use of this set of biomarkers for the diagnosis and prognosis of Venous Thrombosis. As of august 2022, the patent application was filed in the USA and in EU.

A huge effort to develop a product



1. Who we are?
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5. Development of an IVD

Project: example

Project: example

Project: definition

“A temporary endeavor undertaken to create a unique project service or result.”

Project Management Body of Knowledge (PMBOK® Guide), 6° edition

Project: features

Projects are:

- **Temporary.** They have a defined start and closure
- **Unique**, because it generates an outcome that differs from the others;
- They develops by **progressive elaboration** from the refinement of the initial idea.

Project: complexity

- Related to its **management**
- Related to the **technical content**
- Related to **relationships** and **impacts** on people

Source: www.ordingbo.it

Project management

Application of knowledge, skills, tools and techniques,

to ensure the **achievement** of objectives

through the **creation** of deliverables that meet the **needs** of stakeholders.

Project management

- **60s – mid 80s of the 20th century**

aerospace, infrastructure, military

- **mid 80s - early 90s**

cross application. Low cost project management software available

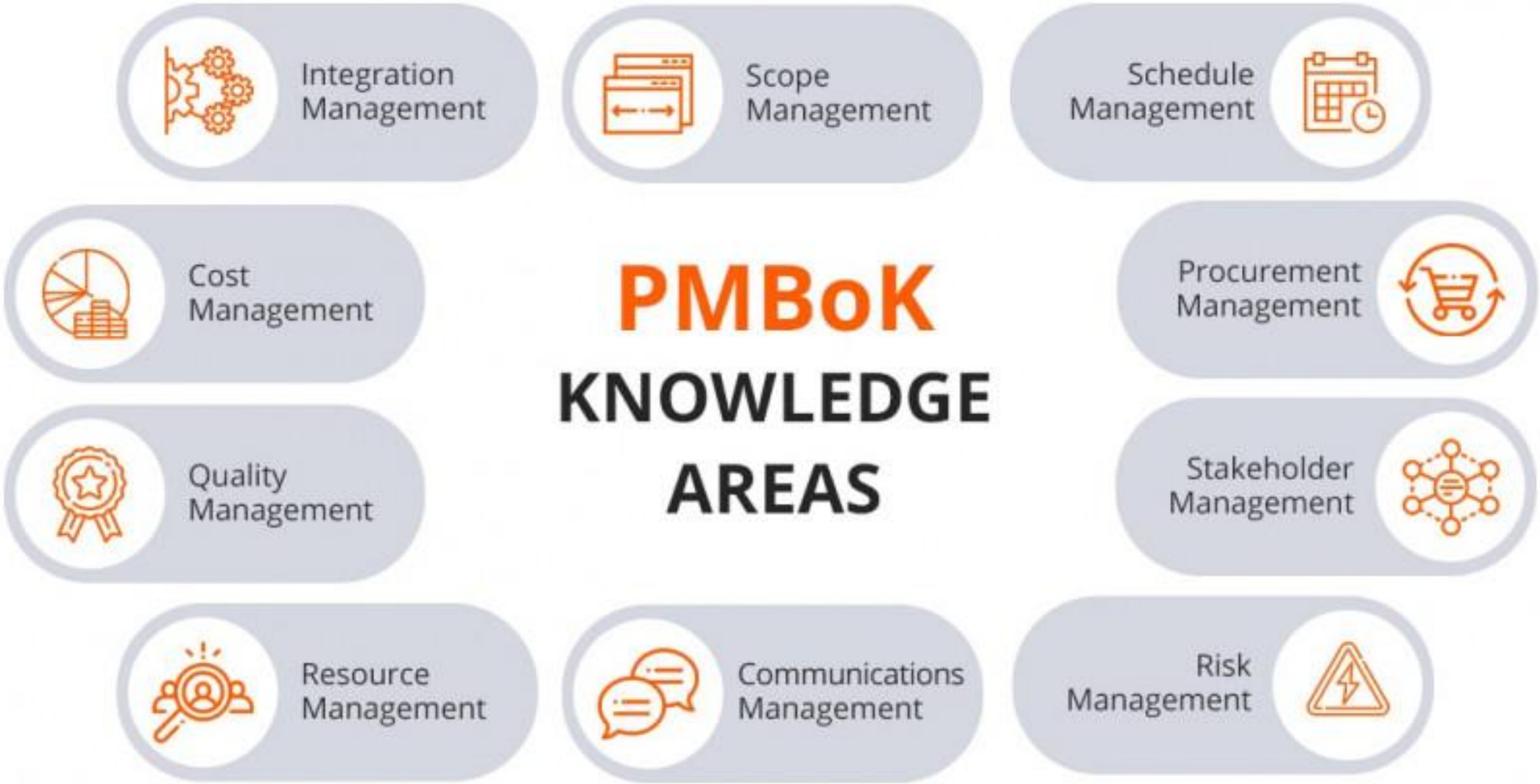
- **early 90s – today**

business orientation (productive, more efficient, and more client oriented; e.g. millennium bug)

Project life cycle

- it consists of a **set of phases**, sequential or partially overlapping, which connect the beginning of the project to its conclusion;
- each phase brings together a **group of activities**, concluded by a decision-making process (gate), with which to move on to the next.
- it differs from the **product life cycle** which, on the other hand, covers the entire path that goes from the conception and development of the product to its disposal.

Project management
10 areas of knowledge



Source: https://monday.com/

Project Management - Knowledge Area Processes Mind Map
Based on PMBOK® Guide - Fifth Edition (English)
Conceptualized & Developed: © Babou Srinivasan

Intended purpose: definition

"'**intended purpose**' means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements or as specified by the manufacturer in the performance evaluation"

Regulation (EU) 2017/746

Intended purpose

Everything starts with a good intended purpose statement.

- **clear, precise and unambiguous**
- **included** in the **labeling**
- needs to be **consistent with the classification** defined by the manufacturer including all claims

Intended purpose: definition

Verb: '**intend**'

'If you intend to do something, you have **decided** or planned to do it

Name: '**purpose**'

the purpose of something is the **reason** for which it is made or done

Intended purpose vs classification

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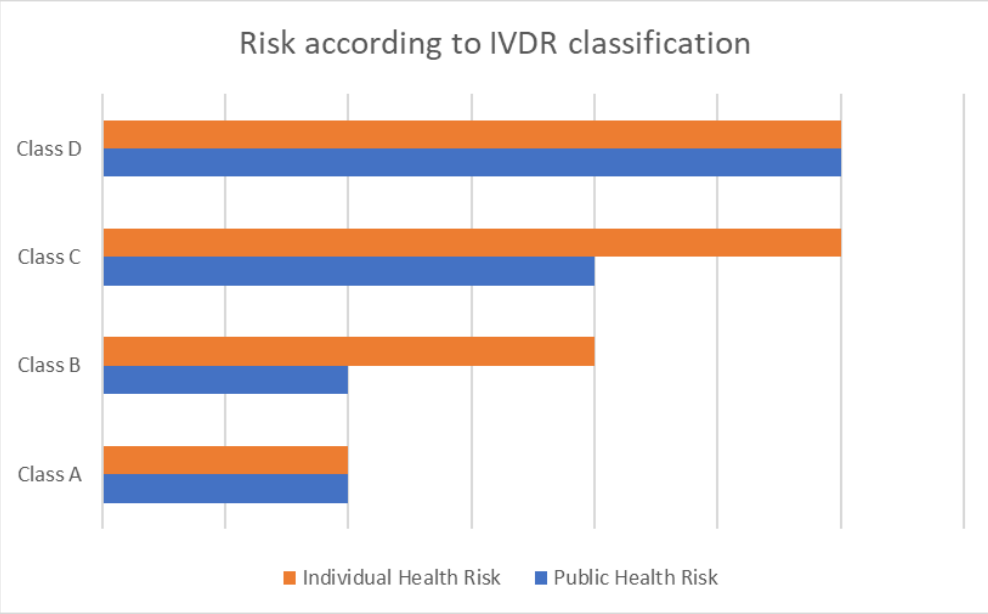

MDCG 2020-16 rev.2

Guidance on Classification Rules for *in vitro* Diagnostic Medical Devices under Regulation (EU) 2017/746

February 2023

Medical Device Coordination Group (MDCG) deals with key issues from the medical devices sector, provide documents to assist stakeholders in applying Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 (IVDR) on in vitro diagnostic medical devices. Not legally binding. They present a common understanding of how the IVDR should be applied in practice aiming at an effective and harmonised implementation of the legislation.

The IVDR class depends on the **intended medical use,** not the specific product features or specifications of the product

Intended purpose: classification

MDCG 2020-16: Different rules help in the definition of the class of the device.

Some examples:

Devices intended to be used for the following purposes are classified as class D:
Devices intended to be used for the detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration
Relevant definitions; - 'devices for screening' - 'detecting the exposure to' - 'detecting the presence of' - 'infective/infectious agent' **RATIONALE** Rule 1; first indent classifies all devices intended to assess the suitability of blood, blood components, cells, tissues or organs or their derivatives for transfusion, transplantation or cell administration, with the respect to transmissible agents. The result of the test will be a major determinant as to whether the analysed donation will be used. Typical devices under this rule are intended for the detection of those agents for which the EU has harmonized the donor and donation testing requirements within the context of risk of transmission of infection (European Directives 2002/98/EC[3], 2006/17/EC[4], 2010/45/EU (corrigendum: 2010/53/EU)[5]). Those agents are listed in the examples below. It is to be noted that: - National legislation of Member States may impose testing of additional transmissible agents in blood, blood components, cells, tissues or organs or their derivatives when intended for transfusion, transplantation or cell administration.

Intended purpose: classification

MDCG 2020-16: Different rules help in the definition of the class of the device.

Some examples:

The following are in class C if they are:

(a) Devices intended for detecting the presence of, or exposure to, a sexually transmitted agent

Relevant definitions;

- 'detecting the exposure to'
- 'detecting the presence of'

RATIONALE

Rule 3a classifies devices detecting agents whose main mode of transmission is sexual. Sexually transmitted infections is a group of infections that may transmit through vaginal, oral and anal sexual intercourse. The agents that cause sexually transmitted infections may pass from person to person in blood, semen, or vaginal and other bodily fluids.

EXAMPLES (non-exhaustive)

Devices intended for the detection of:

- *Chlamydia trachomatis*
- *Haemophilus ducryii*
- Herpes simplex virus 1&2,
- Human papilloma virus (HPV)
- *Neisseria gonorrhoeae*
- *Mycoplasma hominis*
- *Mycoplasma genitalium*
- *Trichomonas vaginalis*
- *Treponema pallidum*
- *Ureaplasma urealyticum,*

NOTE 1: Two parasitic diseases commonly transmitted by oro-anal sexual contact are amebiasis and giardiasis. Their primary mode of transmission is nonsexual in nature, through contact with infected food or water, or faeces. Diagnostic devices intended to determine intestinal infections caused by e.g. Entamoeba histolytica and Giardia lamblia, do not fall under this rule, they are captured under Rule 6.

Intended purpose

Example: Syphilis

Function: screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction or companion diagnostic?

Screening of blood donations for syphilis → Class D device

Diagnosis of syphilis → Class C device

CLASSIFICATION OF IVDS ACCORDING TO IVDR 2017/746

CLASS A

LOW PERSONAL RISK, LOW PUBLIC HEALTH RISK

Examples

- Accessories
- Wash buffers
- Specimen receptacles
- Instruments
- Culture media

CLASS B

MODERATE TO LOW PERSONAL RISK, LOW PUBLIC HEALTH RISK

Examples

- Thyroid, kidney, liver function tests
- Infertility assays
- Clinical chemistry
- Hormones, enzymes, proteins • Inf ammatory markers
- Rheumatology markers
- Self-test devices that are not Class C: pregnancy, fertility, cholesterol and urine tests for glucose, erythrocytes, leucocytes and bacteria

CLASS C

HIGH PERSONAL RISK, MODERATE TO LOW PUBLIC HEALTH RISK

Examples

- Syphilis (diagnosis only)
- Neonatal screening for metabolic disorders e.g. PKU
- Rubella
- Cancer markers (screening and diagnosis)
- Genetic tests
- Companion diagnostics
- Blood glucose meters/strips
- Blood gas analysers
- Self tests
- Cardiac markers
- Tissue typing e.g. HLA

CLASS D

HIGH PUBLIC HEALTH RISK, HIGH PERSONAL RISK

Examples

- Blood donation screening e.g. Syphilis, CHAGAS, HTLV I/II
- Blood grouping ABO, Rhesus (including RHW1), Kell, Kidd and Duffy systems.
- Diagnostic test e.g. HIV 1/2

Medical Devices Regulatory Compliance
Your medical devices in a global market
mdro-consulting.com

Intended purpose: content

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- a general description of the device including its intended purpose and intended users:
- what is to be detected and/or measured
- specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;
- its function such as screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic
- whether it is automated or not
- whether it is qualitative, semi-quantitative or quantitative
- the type of specimen(s) required
- where applicable, the testing population
- the intended user
- in addition, for companion diagnostics, the relevant target population and the associated medicinal product(s)

Regulation (EU) 2017/746

Intended purpose: example

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qualitative/semi-quantitative/quantitative

end user

MM GRAM POS NO STAPH is a qu stic test, intended for professional clinical laboratory users, for the multiplex identification of nucleic acid sequences specific to Gram-p sample type aphylococcus bacteria and/or nucleic acid sequences associated with their non-susceptibility to vancomycin, starting from a positive blood culture of Gram-positive bacteria. The MM GRAM POS NO STAPH cartridge contains all the necessary reagents to perform one single test through a Real Time PCR multiplex analysis in combination with MOLECULAR MOUSE SYSTEM.

targets

MM GRAM POS NO STAPH analyzes method gets: Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus pneumoniae, Enterococcus faecalis, Enterococcus spp., Enterococcu coccus anginosus, Listeria monocytogenes, Bacillus subtilis, Streptococcus spp., vanA, vanB, vanC1, vanC2-3. The ne he targets vanA, vanC1, vanB, vanC2-3 does not exclude the presence of other drug resistance mechanisms.

MM GRAM POS function des a result to support the diagnosis of blood infection with Gram-positive other than Staphylococcus microorganisms and/or their non-susceptibility to vancomycin.

The MM GRAM POS NO STAPH test is intended for combined use with other clinical and analytical results within a diagnostic evaluation defined and regulated by each specific laboratory. MM GRAM POS NO STAPH does not replace traditional methods based on culture and antibiotic susceptibility testing.

The result does not exclude the combined presence of targets other than those included in the list of identifiable targets for the identification of which other independent tests are necessary.

In intended purpose you don’t write the class of the device, but the rationale by which you define the class

Pregnancy test: example

Rapid™ Response

For professional in vitro diagnostic use only.

Human Chorionic Gonadotropin
hCG Test Cassette (Urine)
Product Insert
REF HCG-1C25, HCG-1C50

INTENDED USE

The Rapid Response™ hCG Test Cassette (Urine) is a rapid visual immunoassay for the qualitative, presumptive detection of human chorionic gonadotropin in human urine specimens. This kit is intended for using as an aid in the early detection of pregnancy.

Atlas Medical

CE REF:0459

Atlas Home Pregnancy Midstream Test (Urine)

IVD *For In-Vitro Diagnostic and self-testing use*

2 30°C Store at (2-30° C)

INTENDED USE

The Atlas Home Pregnancy Midstream Test is a rapid one step assay designed for qualitative detection of human Chorionic Gonadotropin (hCG) in urine to aid in the early detection of pregnancy.

Question time!

Project Management - Knowledge Area Processes Mind Map
Based on PMBOK® Guide - Fifth Edition (English)
Conceptualized & Developed: © Babou Srinivasan

Stakeholder: definiton

"an individual, group, or organization who **may affect, be affected by or perceive itself to be affected** by a decision, activity, or outcome of a project"

Project Management Body of Knowledge (PMBOK® Guide), 6° edition

Stakeholders

it is essential to:

- **identify** stakeholders at the beginning of the project
- **analyze** their levels of interest, individual expectations, importance and involvement
- **monitor** their role throughout the duration of the project

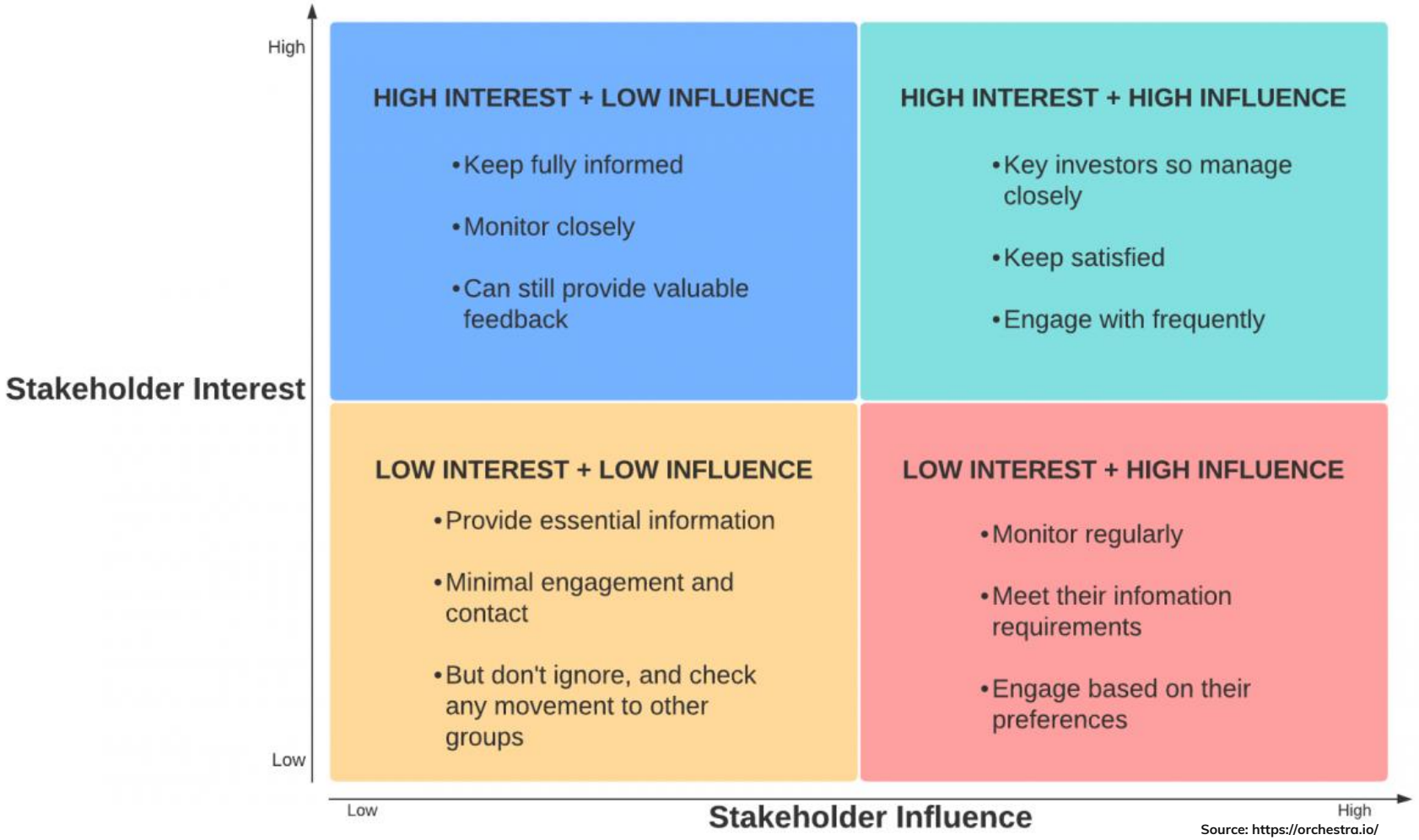
Project Management Body of Knowledge (PMBOK® Guide), 6° edition

Stakeholders engagement

- **Unaware:** unaware of the project and any potential impacts its outcome may have on them
- **Resistant:** aware of the project and are resistant to the change
- **Neutral:** aware of the project but are neither resistant to or supportive of it
- **Supportive:** aware of the project and its potential impact and supportive of the change
- **Leading:** aware of the project and are actively working to ensure its success

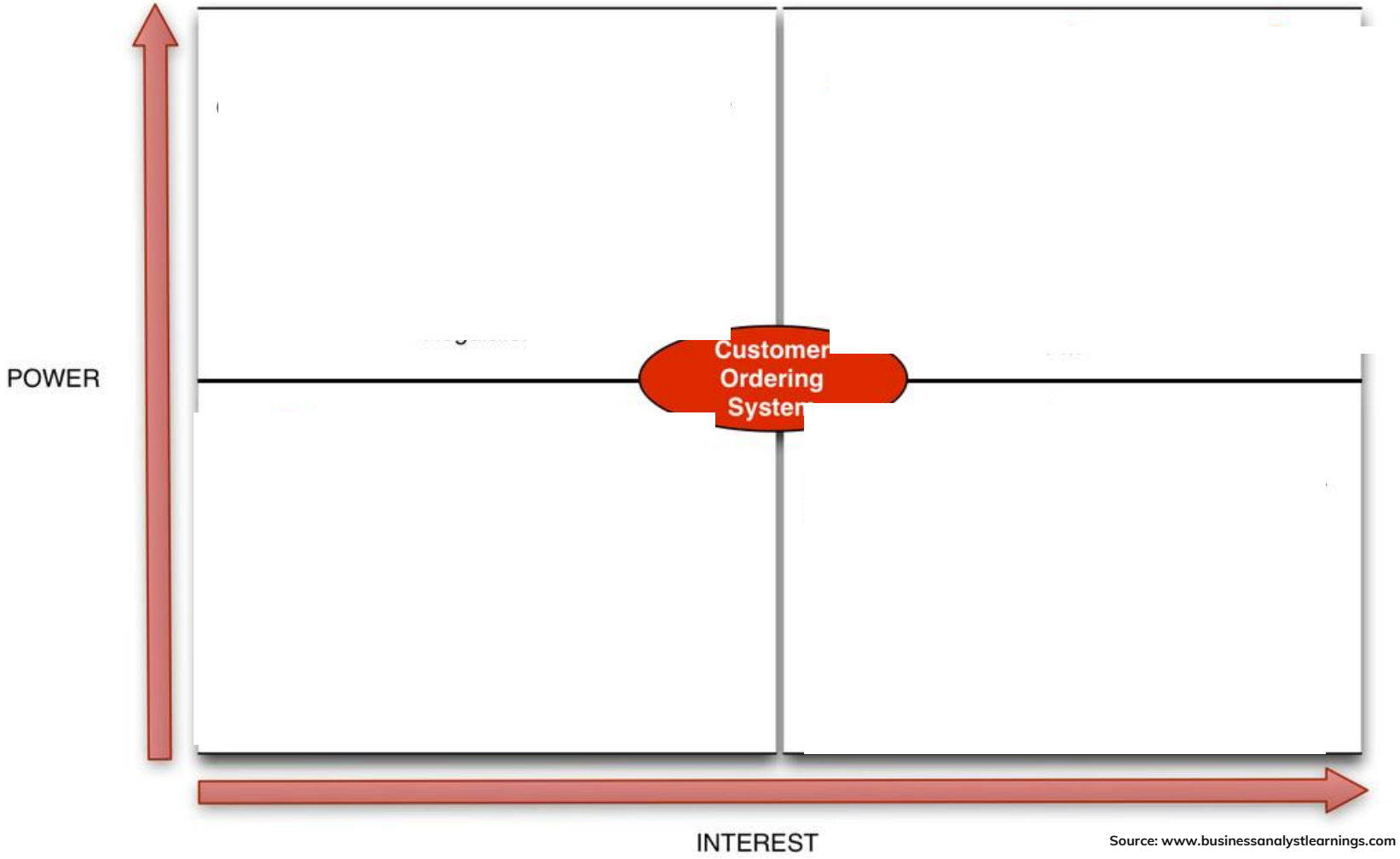
Project Management Body of Knowledge (PMBOK® Guide), 6° edition

Stakeholders assessment matrix



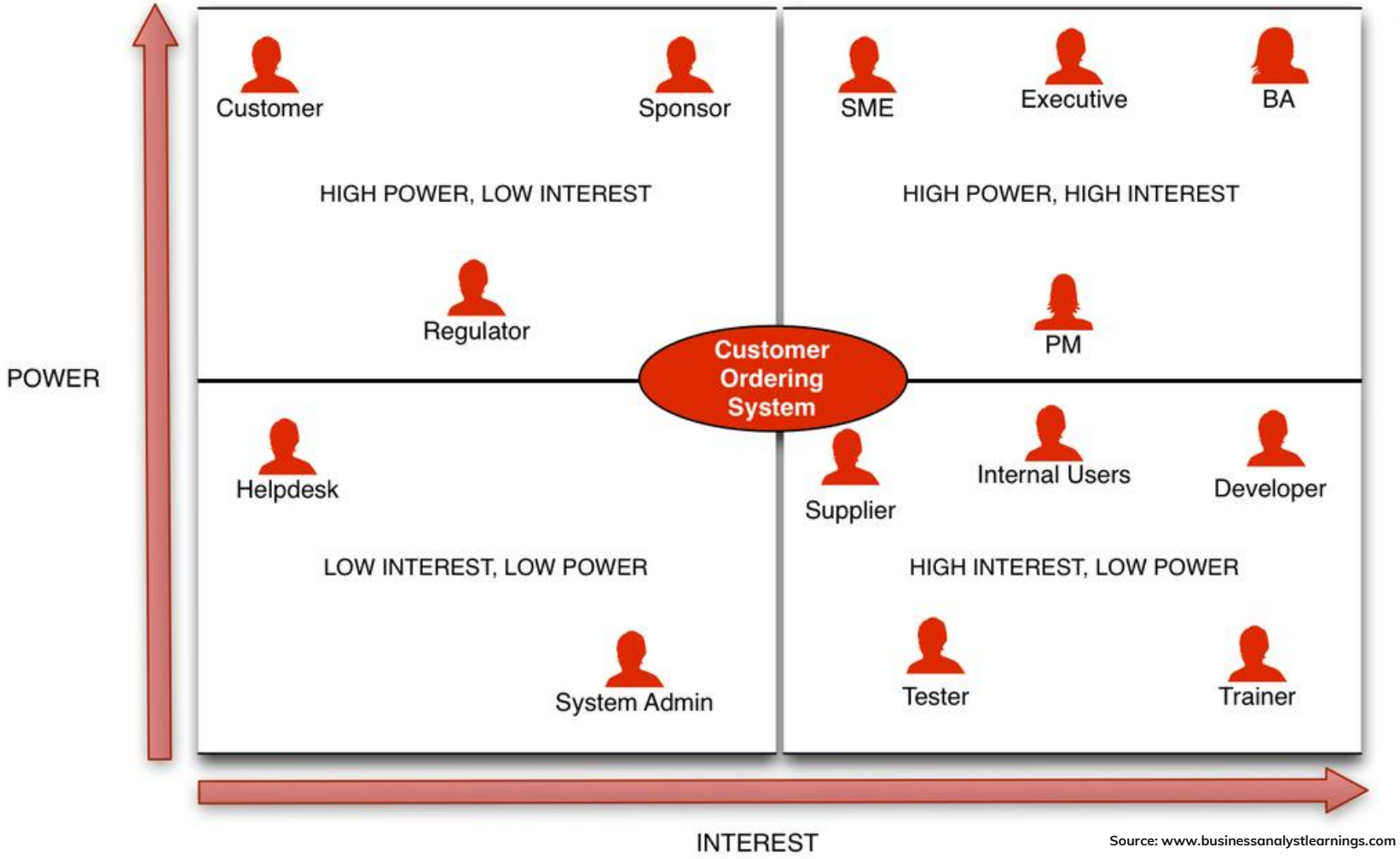
Source: https://orchestra.io/

Stakeholders assessment matrix: An example



Source: www.businessanalystlearnings.com

Stakeholders assessment matrix: An example



Source: www.businessanalystlearnings.com

SME: Small Medium Enterprise
BA: Business analyst
PM: Project Manager

Project Management - Knowledge Area Processes Mind Map
Based on PMBOK® Guide - Fifth Edition (English)
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Risk: generic terms

- it is an **uncertain condition or event** which, if it occurs, has an **impact** (positive or negative) on one or more project objectives.

- it generally produces a **negative impact**, but which can sometimes be **positive** and take the form of an opportunity (in this case the term used is **Benefit**). Managing risks aims to reduce the probability and impact of "negative events", and to increase the probability and impact of "positive events".

Negative Risk: what you can do

- Avoid: eliminate the possibility that the event can occur (e.g. exclude critical parts from the project "scope“)
- Mitigate: reduce the probability of the event (prevention) or the extent of the impact (reaction). (e.g. Design implementation
- Accept: decide not to implement any response
- Transfer: to transfer the risk in question and therefore the related consequences to other subjects (e.g.: taking out an insurance policy)
- Escalate: make the approach to the identified risk systemic (e.g. act on all projects in the company if the risk is common to all)

Benefit: what you can do

- Exploit: attempt to reduce the uncertainty linked to an event that can favor the design outcome. Delivering higher quality resources than planned
- Accept: accepting the possibility of having an opportunity without pursuing it
- Enhance: Increase the probability of the event or the extent of the resulting positive impacts (e.g. implementing pro-active event management)
- Escalate: make the approach to the identified risk systemic (e.g. take action on all projects in the company if the opportunity is common to all)
- Sharing: sharing possible opportunities with third parties to mutual benefit (e.g. enter into partnership agreements).

EN ISO 14971: definitions

Benefit

positive impact or desirable outcome of the use of a medical device on the health of an individual, or a positive impact on patient management or public health

Note: Benefits can include positive impact on clinical outcome, the patient's quality of life, outcomes related to diagnosis, positive impact from diagnostic devices on clinical outcomes, or positive impact on public health.

Risk

combination of the **probability** of occurrence of **harm** and the **severity** of that harm

Harm

injury or damage to the health of people, or damage to property or the environment

Severity

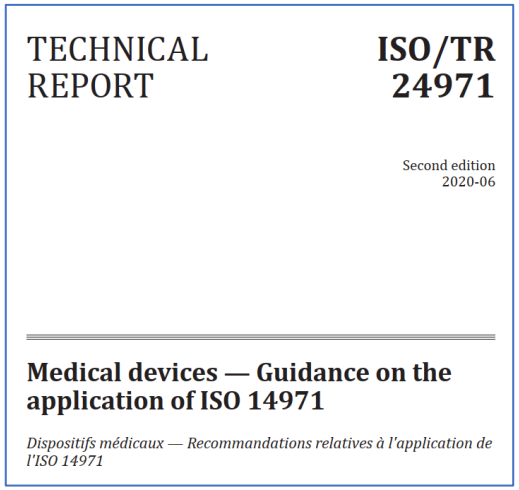
measure of the possible consequences of a hazard

In EN ISO 14971 the term 'risk' is linked to negative impact

EN ISO 14971-Risk evaluation

INSIDE INNOVATION

Element	Steps
Risk Analysis	1. Identify intended use and reasonably foreseeable misuse
	2. Identify characteristics related to safety


TECHNICAL REPORT

ISO/TR 24971

Second edition
2020-06

Medical devices — Guidance on the application of ISO 14971

Dispositifs médicaux — Recommandations relatives à l'application de l'ISO 14971

Hazard Category	Hazard	Hazardous Situation	Potential Harm
Electrical Energy	Leakage Current	User is exposed to leakage current <=1 mA and breaking electric conduction path is likely	Electric Shock - Faint tingle of electricity

Hazard

potential source of harm

Hazardous situation

circumstance in which people, property or the environment is/are exposed to one or more hazards

Harm

injury or damage to the health of people, or damage to property or the environment

EN ISO 14971-Risk evaluation on product

INSIDE INNOVATION

Hazard	Foreseeable sequence of events	*Hazardous situation*	*Harm*
Electromagnetic energy (high voltage)	(1) Electrode cable unintentionally plugged into power line receptacle	Line voltage appears on electrodes	Serious burns Heart fibrillation

Hazard

potential source of harm

Hazardous situation

circumstance in which people, property or the environment is/are exposed to one or more hazards

Harm

injury or damage to the health of people, or damage to property or the environment

EN ISO 14971-Risk evaluation on product

INSIDE INNOVATION

Hazard

potential source of harm

Hazardous situation

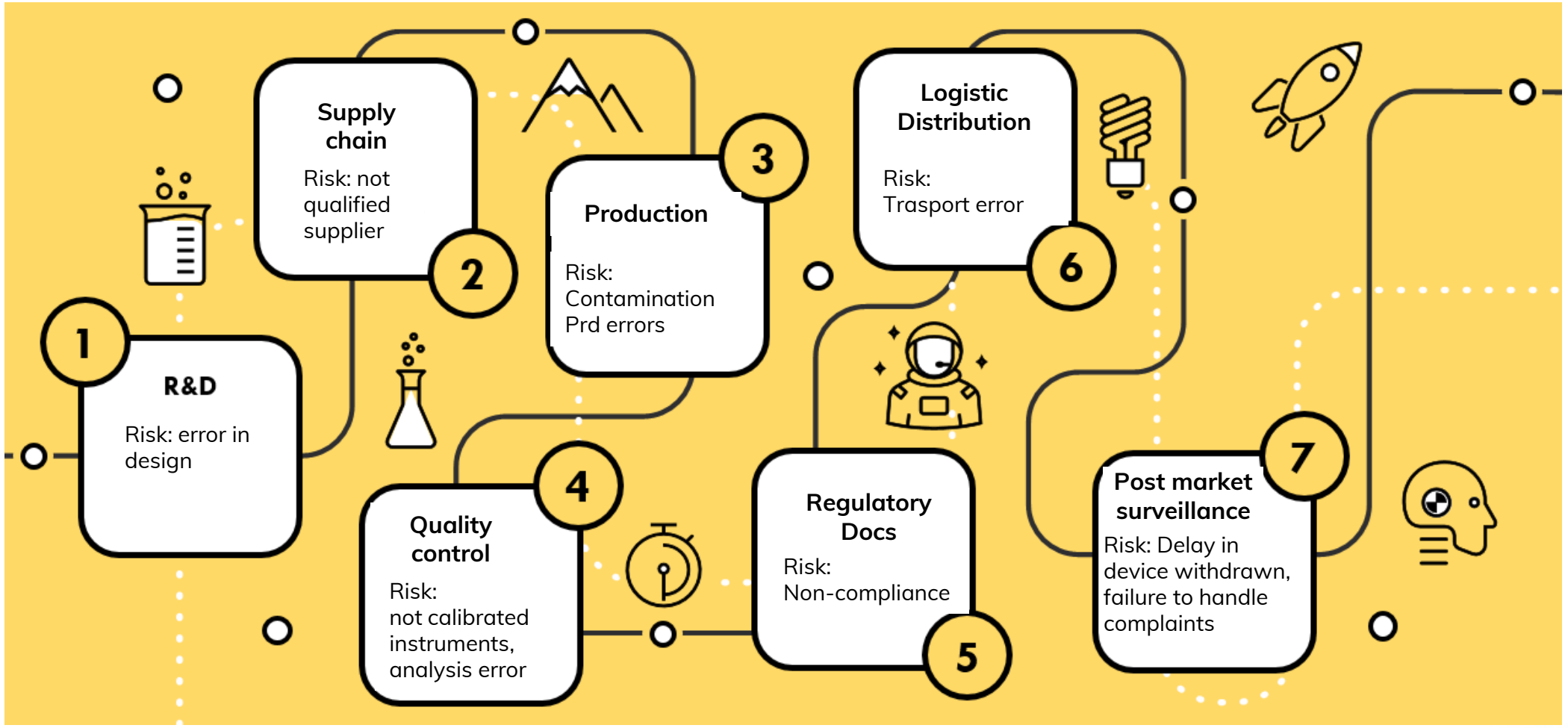
circumstance in which people, property or the environment is/are exposed to one or more hazards

Harm

injury or damage to the health of people, or damage to property or the environment

Hazard	Foreseeable sequence of events	*Hazardous situation*	*Harm*
Electromagnetic energy (high voltage)	(1) Electrode cable unintentionally plugged into power line receptacle	Line voltage appears on electrodes	Serious burns Heart fibrillation
Chemical (volatile solvent, embolus)	(1) Incomplete removal of volatile solvent used in manufacturing (2) Solvent residue converts to gas at body temperature	Development of gas embolism (bubbles in the blood stream) during dialysis	Infarct Brain damage
Biological (microbial contamination)	(1) Inadequate instructions provided for decontaminating re-used anaesthesia tubing (2) Contaminated tubing used during anaesthesia	Bacteria released into airway of patient during anaesthesia	Bacterial infection
Functionality (no delivery)	(1) Electrostatically charged patient touches infusion pump (2) Electrostatic discharge (ESD) causes pump and pump alarms to fail	Failure to deliver insulin to patient with elevated blood glucose level, no warning given	Minor organ damage Decreased consciousness
Functionality (no output)	(1) Implantable defibrillator battery reaches the end of its useful life (2) Inappropriately long interval between clinical follow-up visits	Defibrillator cannot deliver shock when an arrhythmia occurs	Death
Measurement (incorrect information)	(1) Measurement error (2) No detection by user	Incorrect information reported to clinician, leading to misdiagnosis and/or lack of proper therapy	Progression of disease Serious injury

EN ISO 14971-Risk evaluation on process



Risk management

Risk management is a process

Source https://www.lucidchart.com/

Source https://www.kent-playground-inspections.co.uk/

EN ISO 14971: Risk acceptability

Calculation of risk as the product of damage severity and likelihood

Risk index = Severity x Likelihood

Risk value	Acceptability
< chosen value (e.g. 5)	Acceptable
≥ chosen value (e.g. 5)	Not acceptable

For example, a company decides on the following policy:

If the risk is not acceptable the project should be abandoned

Risk management

Let's do some math!

Risk mitigation activities to:

- remove the risk
- mitigate the risk
- act on harm likelihood

Consequences / Severity

Score	1	2	3	4	5
Description	Insignificant	Minor	Moderate	Major	Catastrophic
Example	Minor injury, no first aid required	Harmful injury (first aid required, under 3 days recovery time)	Serious injury, medical assistance required. Injury must be reported	Major injury, urgent medical assistance required	Fatality

Likelihood

Score	1	2	3	4	5
Description	Rare	Unlikely	Possible	Likely	Almost certain

Risk matrix

Consequences / Impact							
	Catastrophic	5	5	10	15	20	25
	Major	4	4	8	12	16	20
	Moderate	3	3	6	9	12	15
	Minor	2	2	4	6	8	10
	Insignificant	1	1	2	3	4	5
			1	2	3	4	5
			Rare	Unlikely	Possible	Likely	Almost certain
Likelihood / Probability							

EN ISO 14971: Acceptability risk matrix

INSIDE INNOVATION

CLOSE

Risk Acceptability Matrix

RISK ACCEPTABILITY MATRIX LOCKED

Probability	Negligible	Minor	Serious	Major	Critical
Frequent 1 in 100	High Requires BRA	High Requires BRA	High Requires BRA	High Requires BRA	High Requires BRA
Probable 1 in 1000	High Requires BRA	High Requires BRA	High Requires BRA	High Requires BRA	High Requires BRA
Occasional 1 in 10,000	Low	Low	High Requires BRA	High Requires BRA	High Requires BRA
Remote 1 in 100,000	Low 2	Low	Low 2	High Requires BRA	High Requires BRA
Improbable 1 in 1,000,000	Low 41	Low 18	Low 12	Low 43	Low 2
	No or negligible risk to patient	Slight customer inconvenience; little to no effect on product performance, non-vital fault	Short-term injury or impairment requiring additional medical intervention to correct (e.g. reoperation)	Severe, long-term injury; potential disability	Loss of limb; life-threatening injury

Severity

BRA = Benefit-Risk Analysis Assessment Incomplete Not Accepted Accepted With BRA Accepted With Design Controls

Source: https://alifax.greenlight.guru/

EN ISO 14971: Risk acceptability

Calculation of risk as the product of damage severity and likelihood

Risk index = Severity x Likelihood

Risk value	Acceptability
< chosen value (e.g. 5)	Acceptable
≥ chosen value (e.g. 5)	Not acceptable

For example, a company decides on the following policy:

If the risk is not acceptable, the risks/benefits should be assessed.

If the risk outweighs the benefit, the project should be abandoned.

UNI EN ISO 14971: Risk benefit analysis

A risk/benefit analysis is not required by this International Standard **for every risk**.

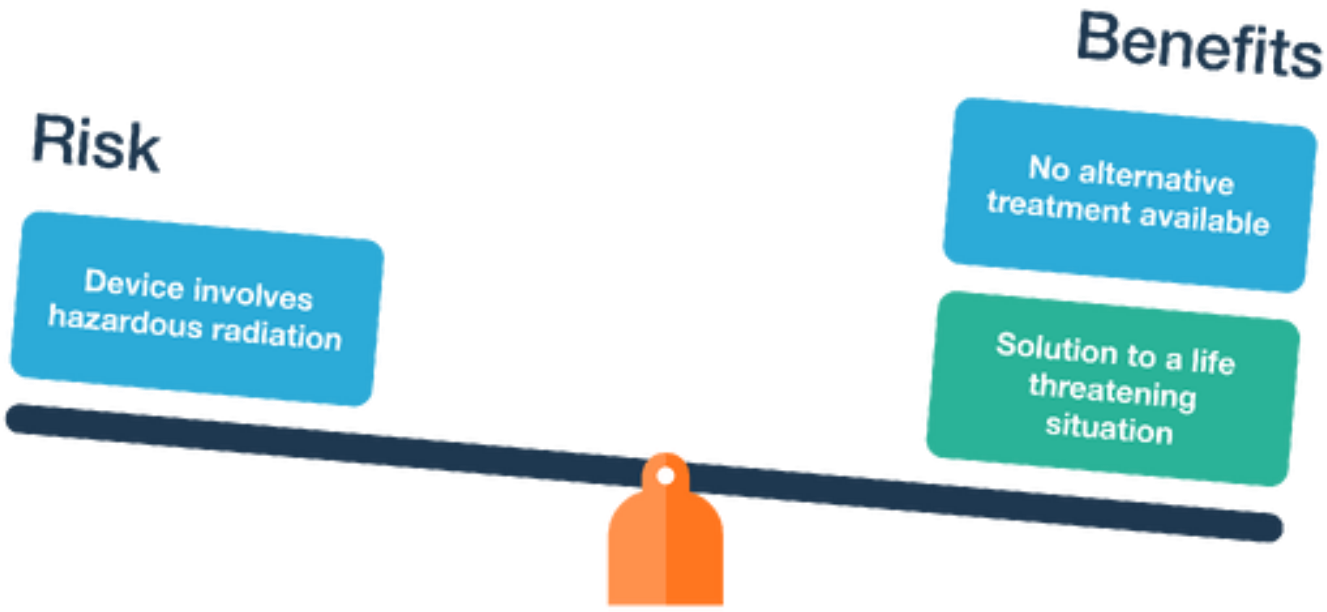
The **risk/benefit analysis** is used **to justify a risk once all the** precautions and feasible measures to reduce the risk **have been applied**. If, after applying these measures, the risk does not is still judged to be acceptable, a risk/benefit analysis is needed to determine whether the medical device provides more benefits than harm.

In general, if all practicable risk control measures are insufficient a meet the risk acceptability criteria in the risk management plan, the project must be abandoned. In some cases, however, higher risks may be justified if they are outweighed by the anticipated benefits of using the device.

UNI EN ISO 14971: Risk benefit analysis

Risk management to weight benefits and decrease risks as much as possible!

UNI EN ISO 14971: Risk benefit analysis



Source: https://blog.sierralabs.com/

Note: benefits do not include economic or business advantages, but mainly clinical benefits

EN ISO 14971: Risk mitigation

To reduce risks, the manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable

risk control

process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

residual risk

risk remaining after risk control measures have been implemented

EN ISO 14971: Risk mitigation

To reduce risks, the manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, manufacturers shall, in the following order of priority:

a) **eliminate** or **reduce** risks **as far as possible** through safe design and manufacture

b) where appropriate, take adequate **protection** measures, including alarms if necessary, in relation to risks that cannot be eliminated

c) **provide information** for safety (warnings/precautions/contra-indications) and, where appropriate, training to users.

Manufacturers shall inform users of any **residual risks**

Risk management

Source: https://marketbusinessnews.com/

Source: Singh et. Al, Trends in Development of Medical Devices, 2020

Is the residual risk acceptable??

Risk management – let's think about!

INSIDE INNOVATION

Examples of risk control measures

Medical device	*Hazard*	*Hazardous situation*	Inherently safe design	Protective measure	Information for *safety*
Syringe (for single use)	Biological contamination	Reuse after previous use on another patient	Self-destruction after use	Clear indication of first use	Warning against reuse
Implantable pacemaker	Loss of functionality	Pacemaker stops functioning due to early battery depletion	Reliable long-life batteries	Alarm before battery depletion	Information on typical battery lifetime
Mechanical patient ventilator	Air pressure	Software failure causes excessive pressure in patient airway	Blower incapable of delivering high pressure	Over-pressure valve in ventilator or in breathing hose	Instruction to use only breathing hose delivered by manufacturer
IVD blood analyser	Systematic error or bias	Incorrect result reported to clinician	Self-calibration	Metrologically traceable calibrators provided	Instruction to verify calibration with trueness control
X-ray equipment	Ionising radiation	Staff exposed to stray radiation	Not feasible (stray radiation always occurs)	Lead shields and lead aprons	Information on radiation level in occupancy zone

ISO/TR 24971:2020

Question time!

1. Who we are?
2. What is an *In Vitro Diagnostic* device
3. Academy vs Company
4. Project management
5. In Vitro Diagnostic device development

ALIFAX R&D: FROM R&D TO CE-IVD

INSIDE INNOVATION

BASIC RESEARCH → FEASIBILITY → PLANNING → PROTOTYPE → PRE-SERIES → VALIDATION → REGULATORY APPROVAL & LAUNCH

INTERNATIONAL STANDARD **ISO 13485**

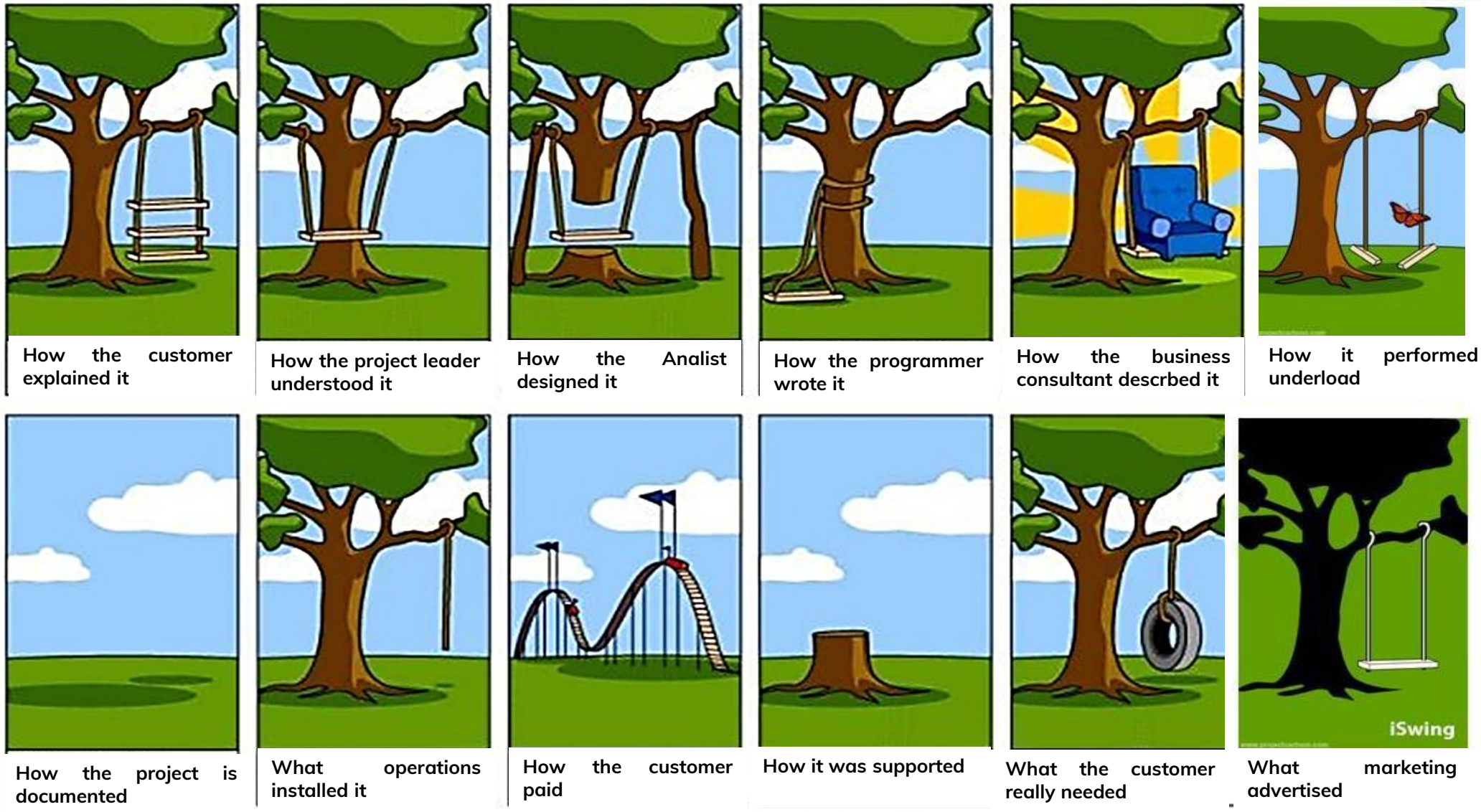
Medical devices — Quality management systems — Requirements for regulatory purposes

Third edition
2016-03-01


CERTIFICATE

A company that develops and manufacture a **CE-IVD** is **ISO 13485** certified.

What is the ‘User need’?

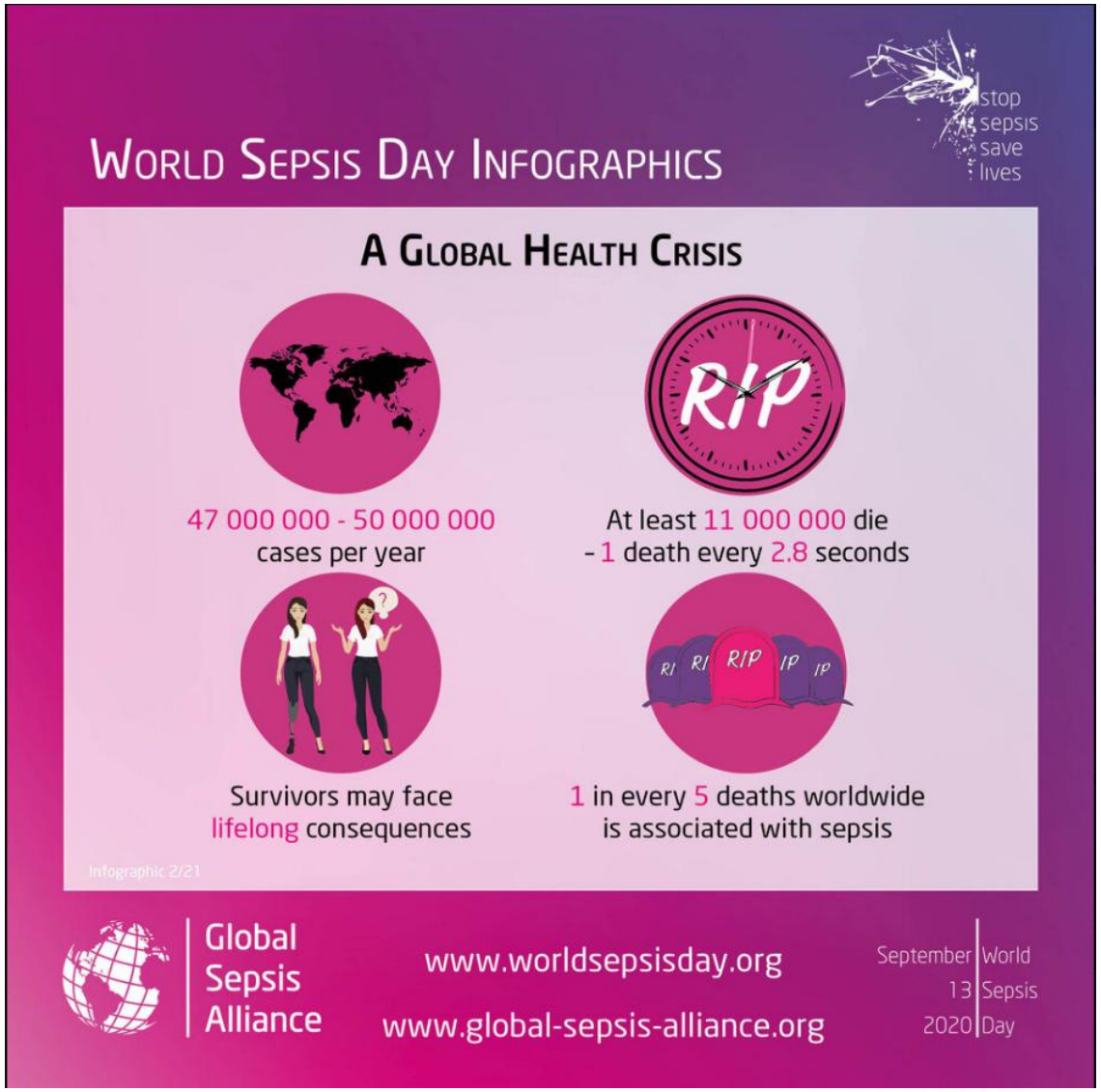


SEPSIS

In case of sepsis, for **every hour** of inappropriate therapy, **mortality rises by 7,5%.**

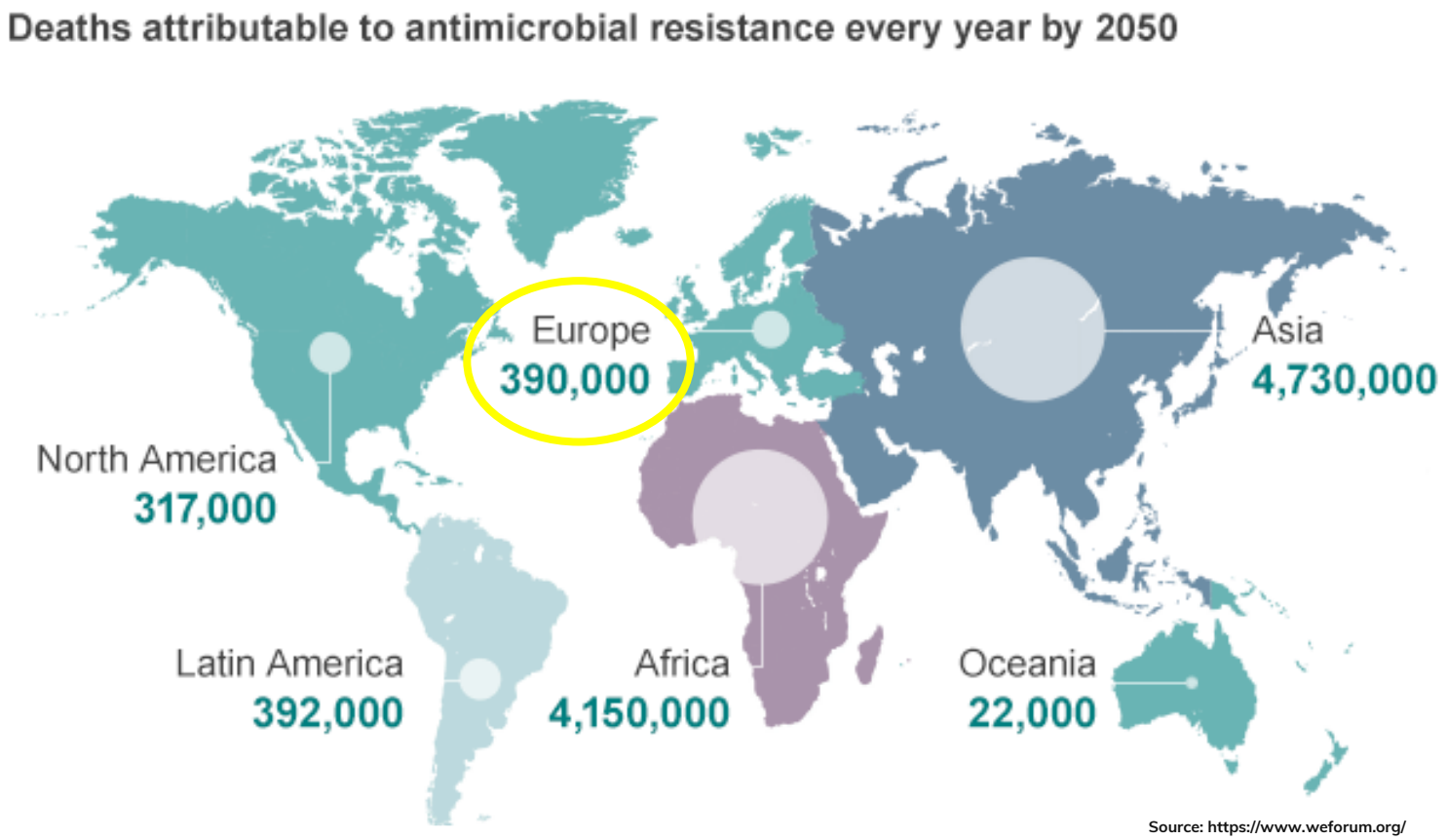
Early diagnosis can lower sepsis-related deaths.

Now that more scientific data are available on COVID-19, the Global Sepsis Alliance can more definitively state that **COVID-19 does indeed cause sepsis.**



WHY IS ANTIMICROBIAI RESISTANCE A GLOBAL CONCERN?

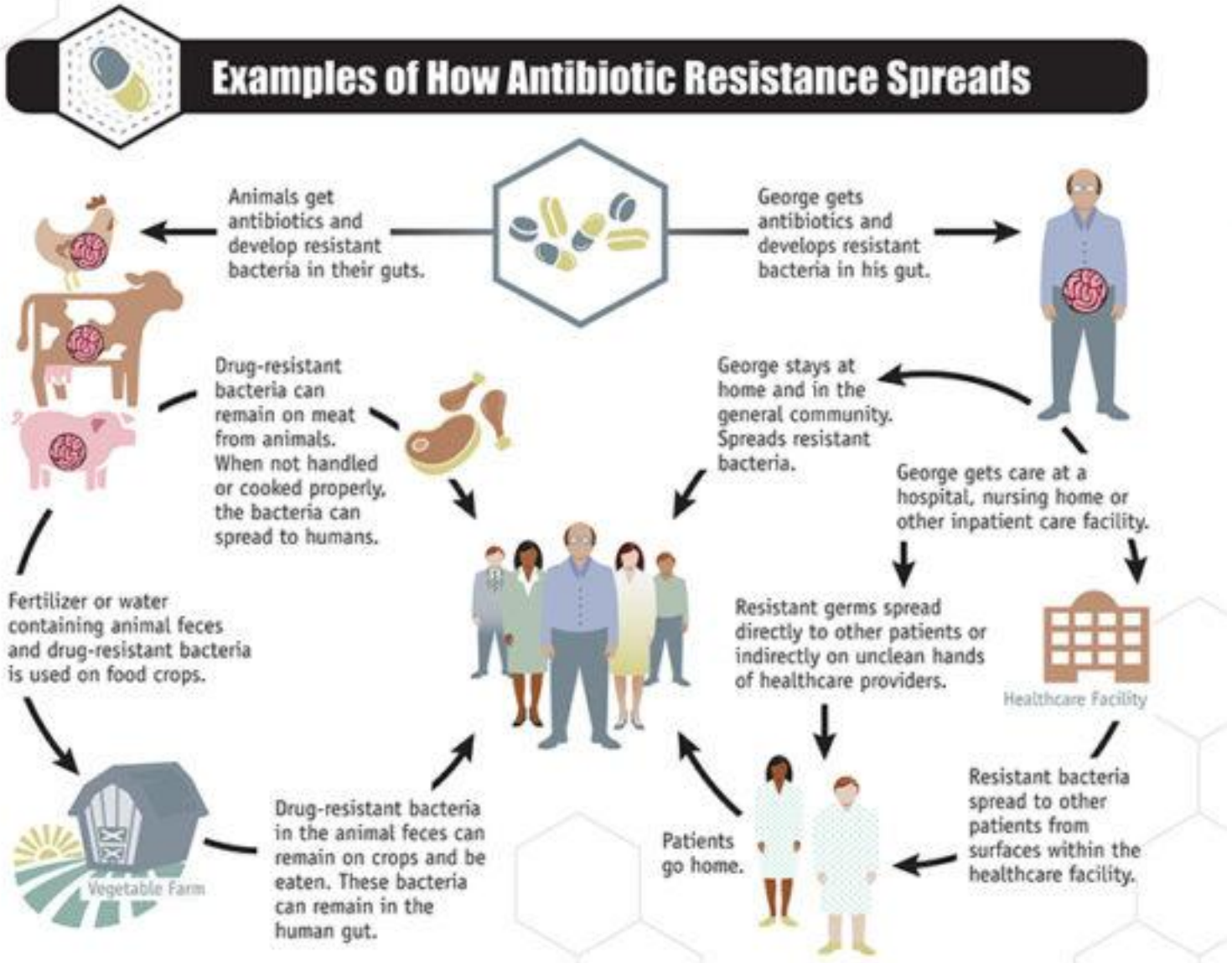
INSIDE INNOVATION



Source: https://www.weforum.org/

2.4 Million people could lose their lives in Europe, North America And Australia in the period 2015-2050. According to the forecasts, Italy, Greece and Portugal would rank among the top of OCSE countries for the highest mortality rates from AMR

According to the forecasts of the World Bank, the economic impact of the AMR could exceed that of the financial crisis of 2008-2009.

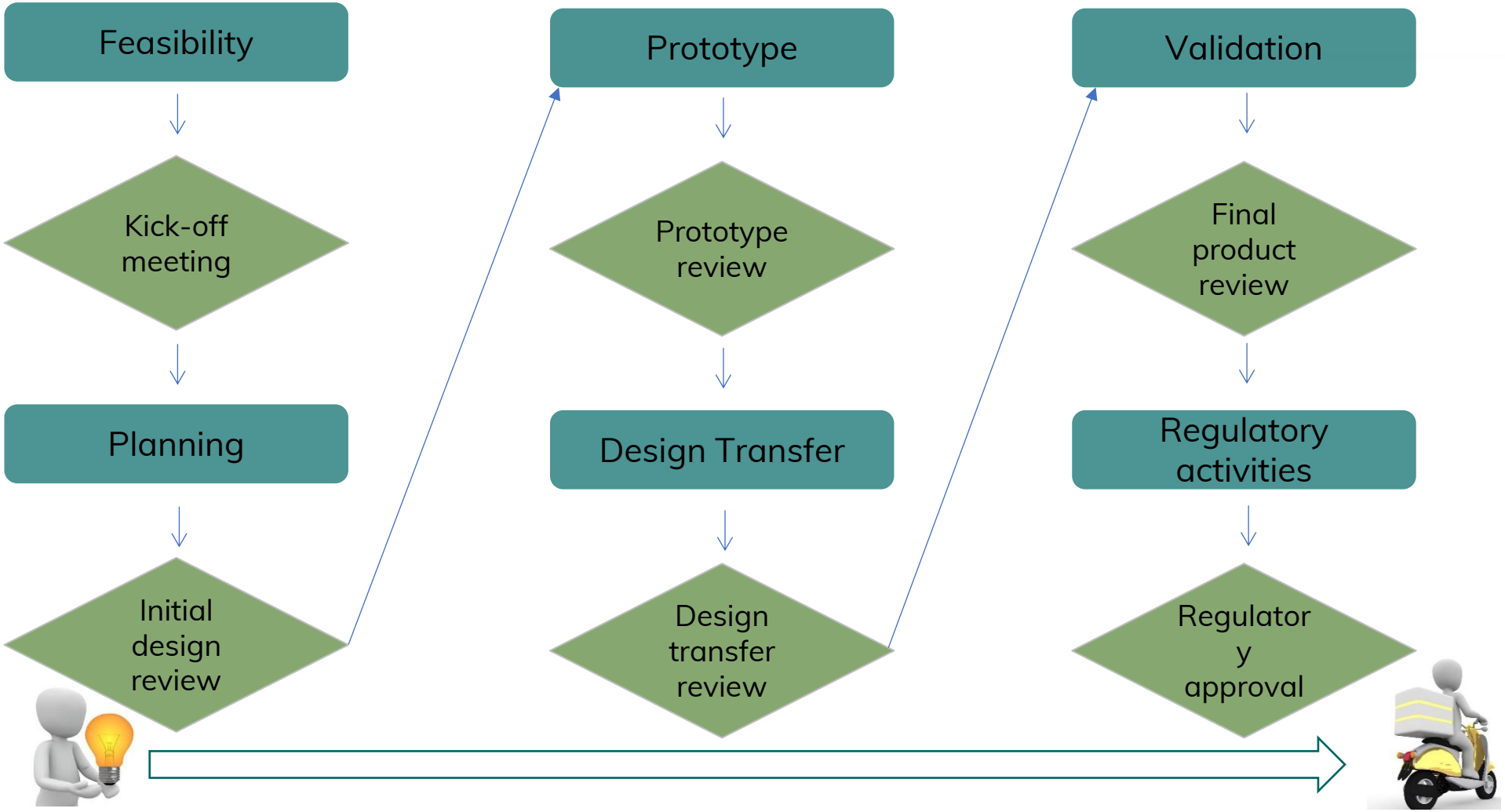


Simply using antibiotics creates resistance. These drugs should only be used to treat infections.

Source: https://www.nfid.org/

From R&D to CE-IVD

INSIDE INNOVATION



Feasibility

Can we answer to user need through a product?

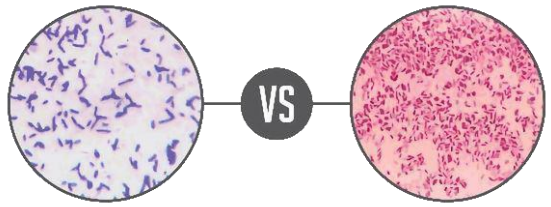
- Technology
- Competitor
- Peculiarity
- No patent infringement
- Costs of production
- External contribution?

SEPSIS: CURRENT TESTS

18 – 32 H

Time consuming

Positive blood culture



Gram Staining

Sub-culture → Phenotypic Test

Bacterial ID and AST

Genotypic Test 2H

Money consuming

Highly specialized user

MOLECULAR MOUSE PLATFORM

INSIDE INNOVATION

1

INSTRUMENT

2

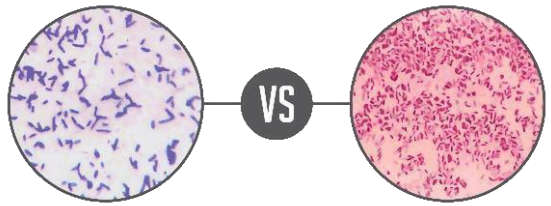
Lab-on-Chip
CARTRIDGE

3

SOFTWARE

SEPSIS: ALIFAX SOLUTION

Positive blood culture



Gram Staining

Gram +

MM GRAM POS STAPH
Code SI 1701.0103

MM GRAM POS NO STAPH
Code SI 1701.0104

Gram -

MM GRAM NEG ID
Code SI 1701.0102

MM GRAM NEG RES
Code SI 1701.0101

Yeast

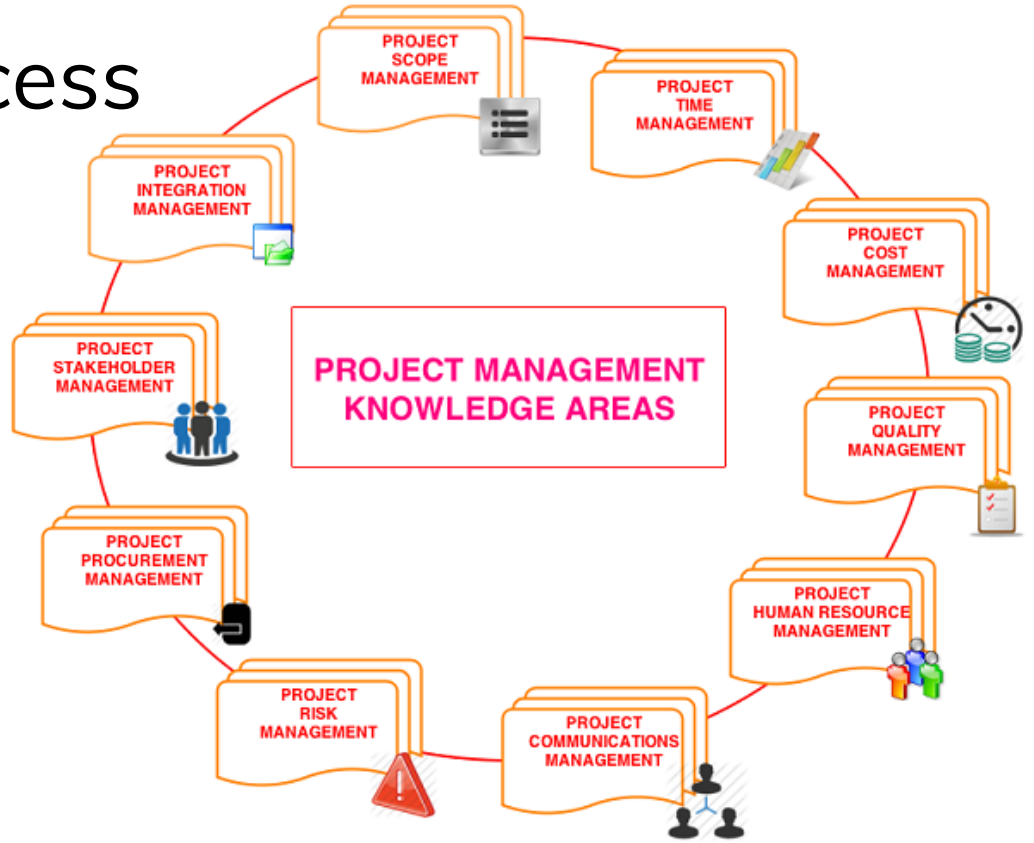
YEAST BLOOD
Code SI 1701.0105

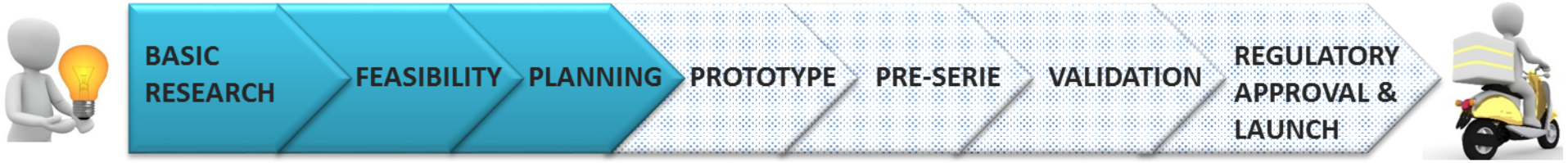
> 1 HOURS

Planning

Planning as the key of success

- Intended use
- Team: roles and responsibility
- Safety
- Risks
- Design input
- Traceability





Sepsis panel cartridges

INSIDE INNOVATION

Intended purpose content

- in vitro diagnostic test
- end user = professional clinical laboratory users
- function = aid to diagnosis
- method = Real Time PCR multiplex analysis in combination with MOLECULAR MOUSE SYSTEM
- test output = qualitative
- specimen= positive blood culture
- aim = identification of nucleic acid sequences specific to microorganisms and/or nucleic acid sequences associated with their non-susceptibility to antibiotics
- aim = microorganisms list and/or nucleic acid sequences associated with their non-susceptibility to antibiotics

Planning: Where to start from?

- Carefully study epidemiology – keep an eye on the area where do you want to sell your product
- Role of opinion leaders
- What do competitors do? (products, product features…)
- What is missing in the market?
- 510K: a foundamental tool to understand how competitors do!

FDA CLEARED

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

Design Traceability Matrix

Product Development Process Phase	Purpose
Planning	Identify scope of the project
User Need	Define user needs (requirements)
Design Input	Define and design inputs (product specifications)
Design Output	Identify and establish design outputs and verification methods
Design Verification	To demonstrate the product meets the design inputs
Design Validation	To demonstrate the product meets the user needs
Market Release	To launch product into manufacturing and marketplace

Source: https://www.greenlight.guru/

don’t forget the risk analysis!!!

output of risk analysis = Design Input

Development:

Product Development Process Phase	Purpose
Planning	Identify scope of the project
User Need	Define user needs (requirements)
Design Input	Define and design inputs (product specifications)
Design Output	Identify and establish design outputs and verification methods
Design Verification	To demonstrate the product meets the design inputs
Design Validation	To demonstrate the product meets the user needs
Market Release	To launch product into manufacturing and marketplace

I. Plan: think about what to do to reach the market

II. Do: produce deliverables

III. Check: review deliverables

IV. Act: move forward / backward until you reach the aim

Phase	Deliverable

Planning	• Project Plan
	  ○ Design & Development Plan
	  ○ Product Description (captured in Project Plan)
	  ○ Quality Plan (captured in Project Plan)
	  ○ Regulatory Plan
	• Risk Management Plan

User Needs	• User requirements • System Risk Analysis (Hazard and Source Identification)
Design Input	• Product specifications • System Risk Analysis (Hazard and Source Identification)
Design Output	• Product and Process Design Outputs (drawings, specifications, work instructions, etc.) • Design Verification Plan(s) • System Risk Evaluation • Risk Assessment (product & process) • Device Master record
Design Verification	• Design Verification Report(s) • Design Validation Plan(s) • Manufacturing Plan • Risk Control • Residual Risk Acceptance
Design Validation	• Regulatory Submissions (as necessary) • Revised Manufacturing Plan • Design Validation Report(s) • Risk Control • Residual Risk Acceptance • Risk Management Report
Market Release	• Regulatory Clearances (as necessary) • Transfer to Manufacturing (DMR Index) • Production and Post-Production Risk Management • Revised Risk Management Report

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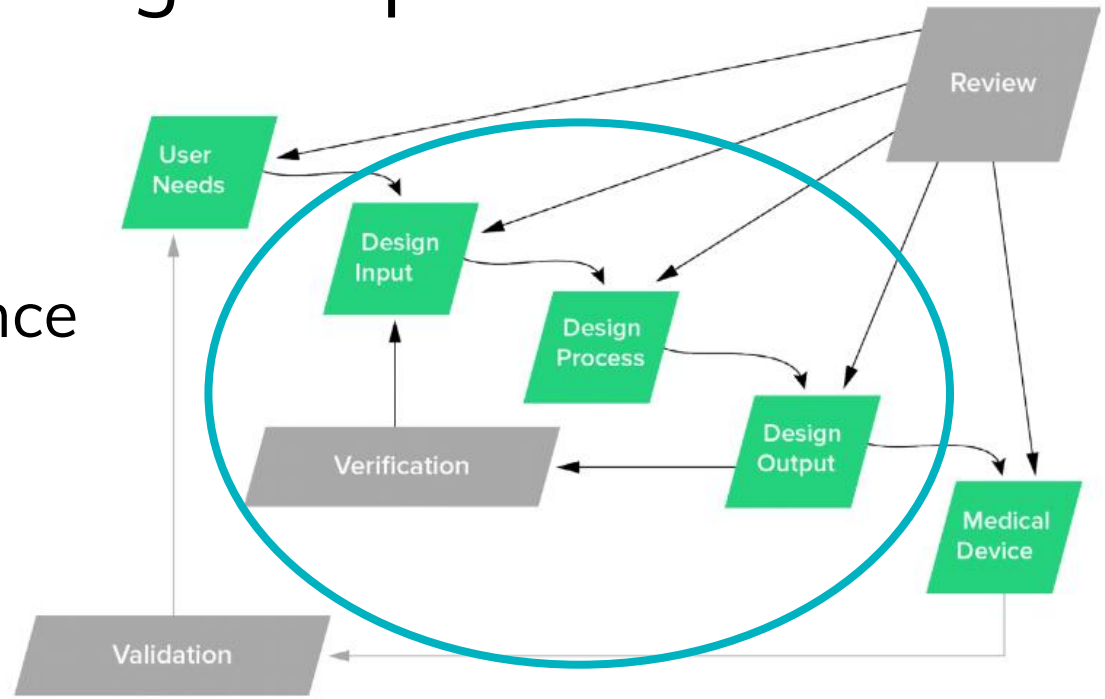
Prototyping

Prototype as a design output to be verified

- Components
- Raw materials
- Criteria of acceptance
- Storage condition
- Stability



Design transfer Pre-series production

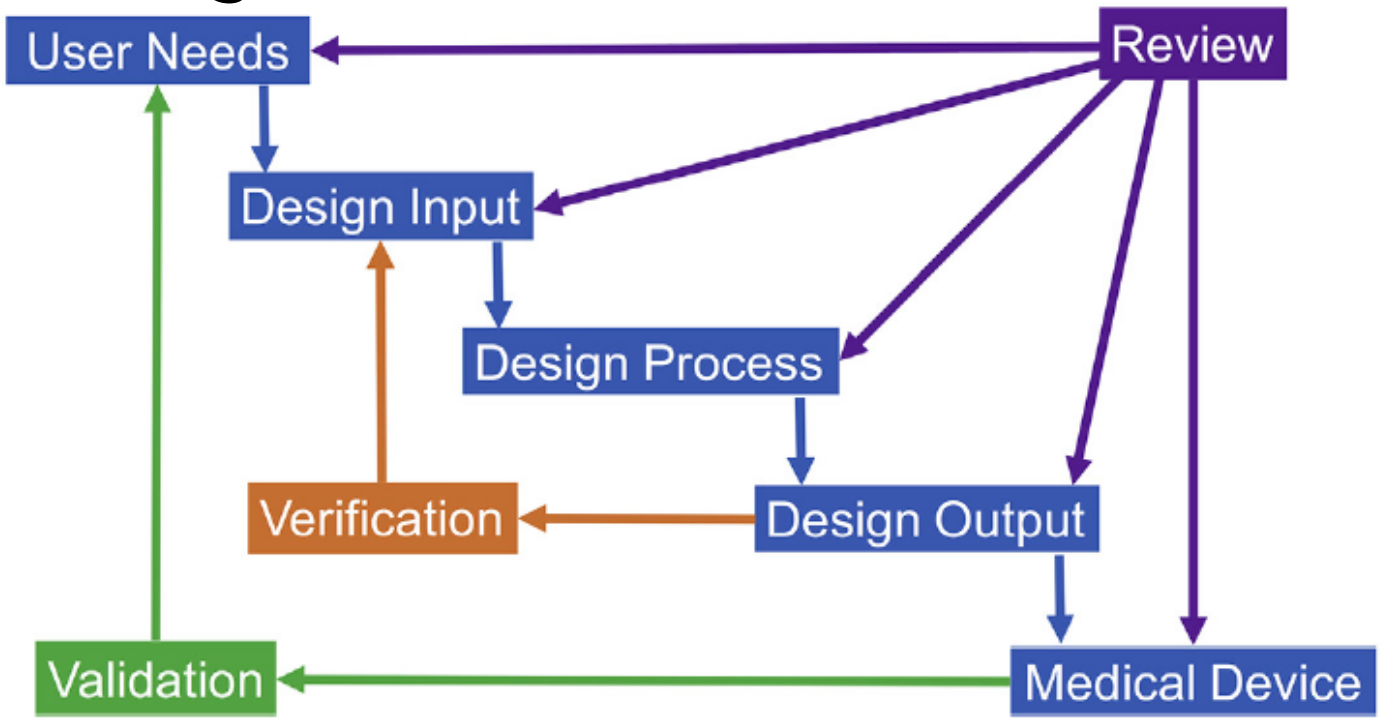
Manufacturing

- Instruction for production
- Quality controls
- Training programs
- Label/packaging
- Installation manual
- Customer documentation

Validation

Is the product answering the user needs?

- Clinical validation
- Process validation



Validation

Is the product answering the user needs?

- Clinical validation
- Process validation

GHTF

- **Key Definitions and Concepts**

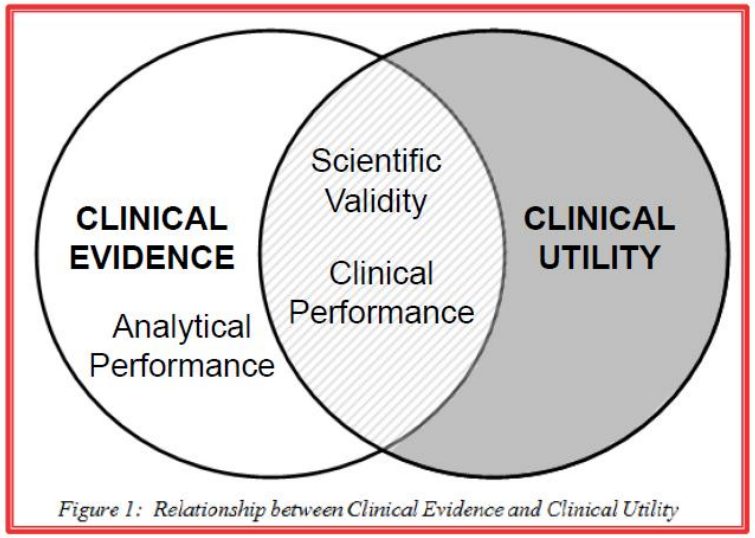


Figure 1: Relationship between Clinical Evidence and Clinical Utility

www.imdrf.org – *GHTF Archive*

Title: Clinical Evidence for IVD medical devices – Key Definitions and Concepts GHTF/SG5/N6:2012 **Date:** November 2nd, 2012

Sepsis panel: Validation plan

INSIDE INNOVATION

Analytical Validation:

1. Analytical sensitivity: limit of detetection (LOD)
2. Reproducibility
3. Analytical specificity (inclusivity and exclusivity)
4. Interference (interfering substances, polimicrobial cultures, blood culture bottle type)

Clinical Validation:

- Sample type: Positive blood cultures (prospective, retrospective, contrived)
- ~ 350-500 specimens (including polymicrobial samples) for each cartridge
- Bottles used in the clinical validation: BACT/ALERT® FN PLUS culture bottles bioMerieux and BACT/ALERT® FA PLUS culture bottles bioMerieux

Sepsis panel: Validation plan

Validation plan: ANALYTICAL VALIDATION

1. Limit of detection (LoD): by testing at least 20 replicates of the lowest dilutions that can produce a positive result, starting from a contrived blood culture specimens at known bacterial concentration (CFU/ml).

LoD = lowest concentration of analyte detected in at least 95% of replicates tested.

FOR EACH BACTERIAL/RESISTANCE TARGET!

2. Reproducibility: aimed to evaluate the agreement between results obtained in independent tests performed with the same sample at the same concentration with different potential sources of variability:

- different operator
- different instrument
- different analysis site
- different testing day
- different cartridge lot

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Sepsis panel: Validation plan

INSIDE INNOVATION

Validation plan: ANALYTICAL VALIDATION

3. Analytical Specificity: aimed to demonstrate the ability of the MM cartridge to identify the desired targets (**inclusivity**), to determine possible cross-reactivity with bacterial samples that are targeted and not targeted by the device (**exclusivity**).

INCLUSIVITY:
Highest available number of on-panel species tested.

- Experimental assays
- *In silico* analysis

EXCLUSIVITY:
Cross-reactivity evaluated testing:

- Contrived blood cultures spiked with certified isolates;
- Clinical positive blood cultures specimens

Sepsis panel: Validation plan

INSIDE INNOVATION

Validation plan: ANALYTICAL VALIDATION

4. Interference: aimed to evaluate the potential inhibitory/interfering effects of different substances/agents/media on MM results.

- ✓ Interfering Substances
  - Endogenous substance:
    hemoglobin, triglycerides, conjugated bilirubin, unconjugated bilirubin, gamma-globulin, human genomic DNA
  - Anticoagulants:
    Sodium citrate, K2EDTA, K3EDTA, Lithium Heparin, Sodium Heparin
  - Disinfectants:
    Bleach 5%, Ethanol 7%

- ✓ Poly-microbial

Microbiological agents found in mixed positive blood culture or contaminants

- ✓ Blood culture bottle types
  - 2 blood culture system (bioMerieux, BD)
  - 3 bottle types/system (FA PLUS, FN PLUS, Pediatric)

Sepsis panel: Validation plan

INSIDE INNOVATION

Validation Plan: CLINICAL VALIDATION

~ 1800 total specimens (including polymicrobial samples)
analyzed in the clinical validations of the 5 Sepsis MM cartridges

~ 1900 total strains analyzed
analyzed in the clinical validations of the 5 Sepsis MM cartridges

64 total targets validated

REFERENCE METHODS: MALDI, antibiogram, genotipic reference method

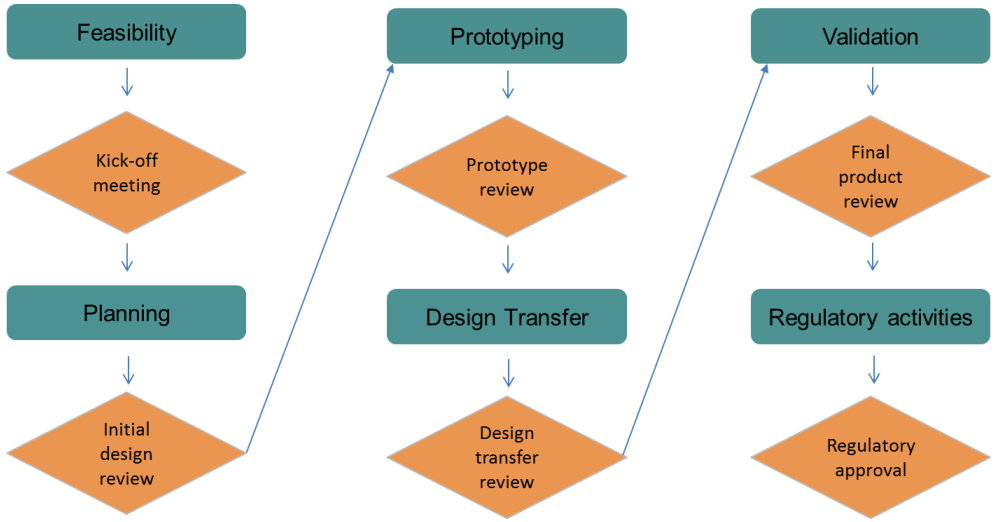
Regulatory closing activities

INSIDE INNOVATION

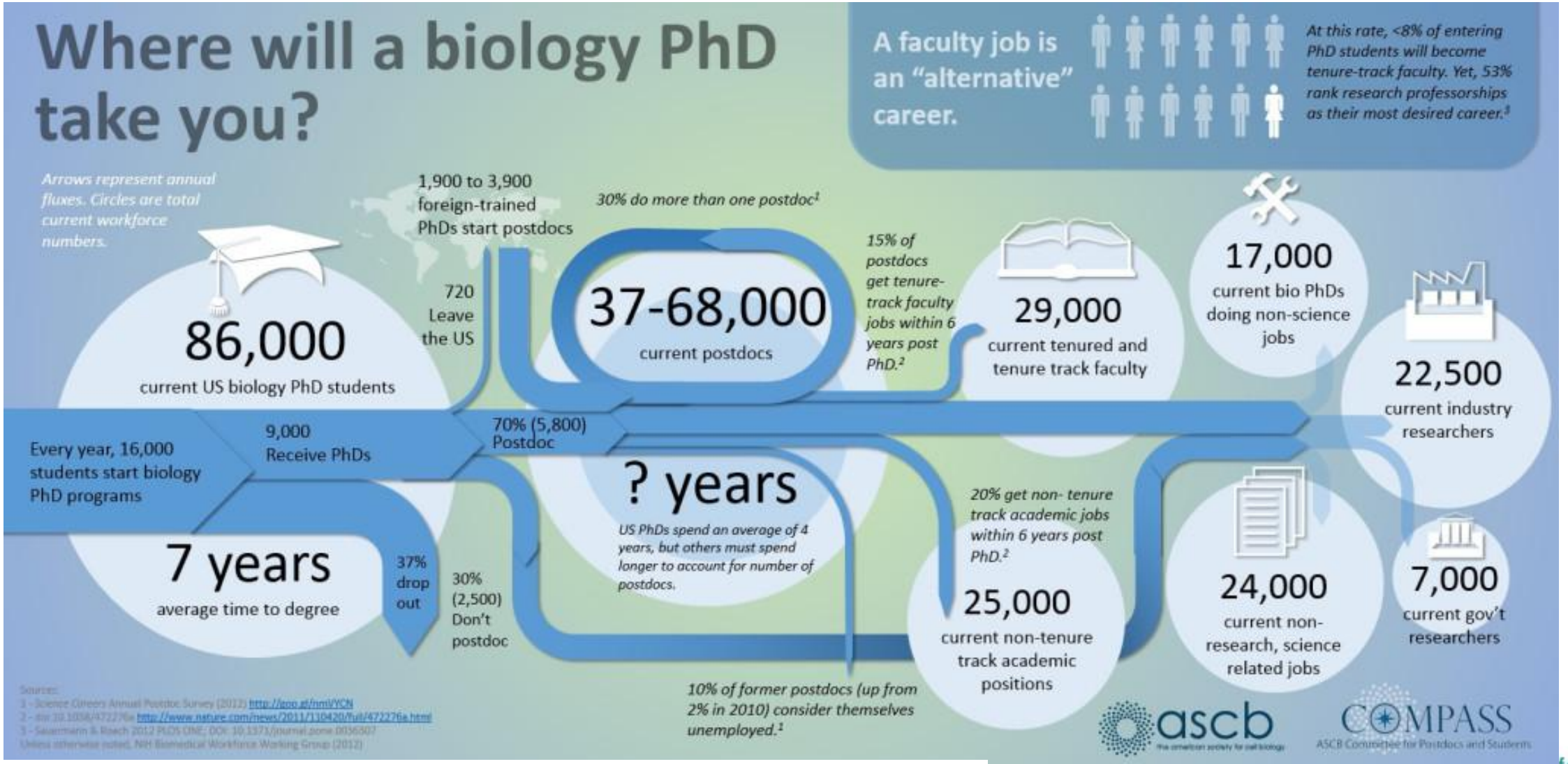
CE-IVD certification to allow commercialization

All the R&D process have to be performed in ‘quality’

- Traceability of process
- Traceability of review
- Notified Body inspection (?)



A lot of opportunities also in companies!




ALI
FAX

Project Management - Knowledge Area Processes Mind Map
Based on PMBOK® Guide - Fifth Edition (English)
Conceptualized & Developed: © Babou Srinivasan

Source: https://www.profit.co/

Project plan: aspects to be defined

Scope of the project

Scope of the project includes project requirements, the vision behind it, measurable goals, outcomes and deliverables, and the activities that can and cannot be done for the successful completion of the project.

Budget and allocation of resources

Budget is one of the most critical aspects of a project. Budget needs to be allocated for different phases, tasks and activities based on their priorities and requirements. Allocating fewer resources for something is equally damaging to the project as allocating more for the same. Project planning carefully weighs different requirements and priorities of the project before determining the budget for each. In addition to the budget, the project also needs other resources, such as manpower, tools and facilities.

Project plan: aspects to be defined

Timelines

Every task and activity in the project takes a certain amount of time for different teams to complete. Adequate time should be given for each, and there should be an estimated timeline for each. Further, a project may be implemented in the long term. So, it may be divided into various phases, which will be deemed complete at the achievement of specific milestones. Project planning involves defining these timelines, creating a schedule for each team and individual, and determining the milestones for various phases of the project.

Process groups

The PMBOK utilizes five process groups to categorize operations of general management needed to run an enterprise or oversee a project.

1. Initiating
2. Planning
3. Executing
4. Monitoring and Controlling
5. Closing

Project Management Body of Knowledge (PMBOK® Guide), 6° edition

Project Plan

1. Iniziating

Processes that **initiate** the beginning of a new project such as identifying a need, addressing a concern, or receiving authorization.

2. Planning

Processes that **establish the initial proposal** of the project such as limiting the scope, communicating the objectives, and defining the actions necessary to achieve them in terms of **time, resources, costs, quality**.

Project Management Body of Knowledge (PMBOK® Guide), 6° edition

Project plan

3. Executing

Processes completed to further the project along- **performing the work** defined in the planning of the project and meeting specifications

4. Monitoring and Controlling

Processes executed that **track** and **review** the development of the project, making changes and extending deadlines as needed.

5. Closing

Processes that quality check all of the work completed for the project and **finalize** it for official use.

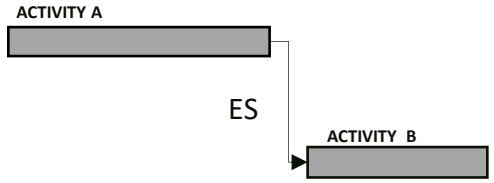
Project Management Body of Knowledge (PMBOK® Guide), 6° edition

Links between the activities

Precedence link End – Start (ES)

B can only start after A is finished

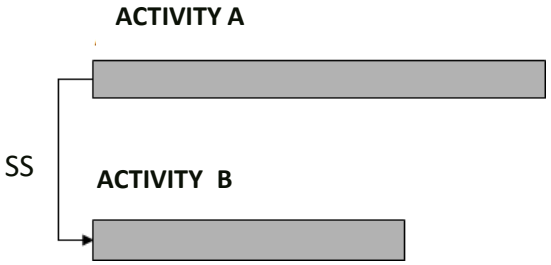
B cannot start until A is finished



Precedence link Start – Start (SS)

B can only start after A has started

B cannot start until A has started

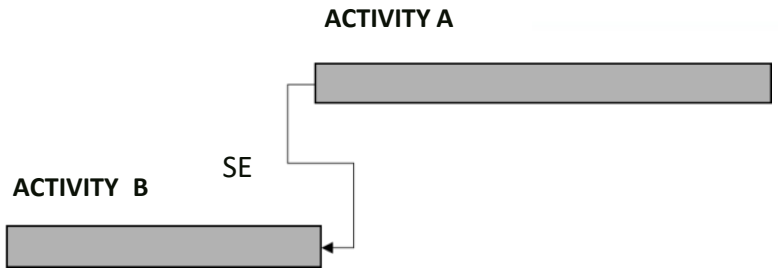


Links between the activities

Precedence link Start – End (SE)

B can only end after A has begun

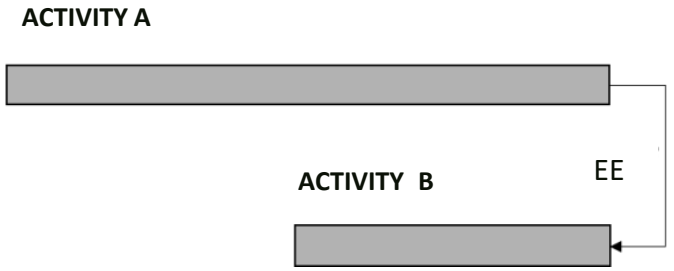
B cannot finish until A has started



Precedence link End – End (EE)

B can only finish after A is finished

B cannot finish until A is finished



Sequence the activities

- **mandatory** (or "rigid logic"), intrinsic to the nature of the work to be performed
- **discretionary** (or "preferred logic", "preferred logic" or "weak logic"), established on the basis of the knowledge of the people who carry out the scheduling, supported by company lessons learned
- **external** as the project activity depends on external activities
- **internal** as the constraints are internal to the project.

Source: https://www.sdu.dk/