Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

The use of off-label data for regulatory decision making

Clinical Studies with Medical Devices and IVDs Conference, Vienna

Tom Melvin
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Director, MSc Medical Device Regulatory Affairs

Agenda

- What is off-label use?
- Why is it important?
- What does MDR and guidance say?
- Why is policy challenging?
- What is needed in Europe, and what is happening?

What is off-label use?

Historical perspective – United States from 1938 to 1976

The FDA's procedural powers over devices were limited to seizure of the misbranded product and prosecution of the producer. It could not initiate regulatory action until a device had entered interstate commerce and then only if it deemed the product ***improperly labeled*** *("****misbranded****") or dangerous ("adulterated").*

Managing the Medical Arms Race, Susan Bartlett Foote

Organization	Definition/Interpretation
Medicines & Healthcare products Regulatory Agency (MHRA), the UK regulating authority1[1]	You should use medical devices as described by the manufacturer in the instructions. If you use the device in any other way, it's considered 'off-label' use
Therapeutic Goods Administration – The Australian Regulating Authority[2]	'Off-label use' generally refers to the use of a therapeutic good for an indication or intended purpose that is not specified in its Australian Register of Therapeutic Goods (ARTG) entry. Therapeutic goods are included in the ARTG with either specific indication(s) or intended purpose(s).
Medical Device Network[3]	Any information that comes with a product is considered labelling and when the product is used for a clinical indication that is not approved, it is regarded as off-label use.

Ref. Team NB position paper, Data generated from 'Off-Label' Use of a device under the EU Medical Device Regulation 2017/745. https://www.team-nb.org/wp-content/uploads/2022/10/Team-NB-PositionPaper-Off-LabelUse-V1-20221005.pdf

Types of off-label use

Different to the intended purpose / intended use

Different to the indications (when a device has one)

Different to other parts of the IFU

Re-use of single use devices if 'opt-in' on national basis (MDR, Article 17)

Why is it important?

Off-label use is essential for some interventions

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Congenital Heart Disease

Pediatric Interventional Cardiology in the United States is Dependent on the Off-label Use of Medical Devices

Jamie S. Sutherell MD, Russel Hirsch MD, Robert H. Beekman, III MD

First published: 20 January 2010 | https://doi.org/10.1111/j.1747-0803.2009.00364.x | Citations: 37

Robert Beekman, III, MD, Division of Cardiology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave. Cincinnati, OH, USA. Tel: 513-636-7072; Fax: 513-636-2410; E-mail: RBeekman@cchmc.org

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ABSTRACT

Objective. A substantial unmet medical device need exists in pediatric care. As a result, the off-label use of approved devices is routine in pediatric interventional cardiology, but the extent and nature of this practice has not been previously described. The purpose of this study, therefore, is to evaluate the prevalence and nature of off-label cardiac device use in an active pediatric interventional program in the United States.

Study Design. This study is a retrospective review of all interventional cardiac procedures performed at our institution from July 1, 2005 to June 30, 2008. Diagnostic (noninterventional) catheterizations, myocardial biopsies, invasive electrophysiology studies, and studies involving investigational devices were excluded. Interventions performed were compared with the manufacturer's labeled indications for each device.

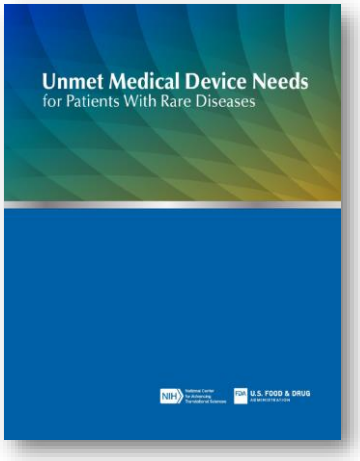
63% of procedures were off-label

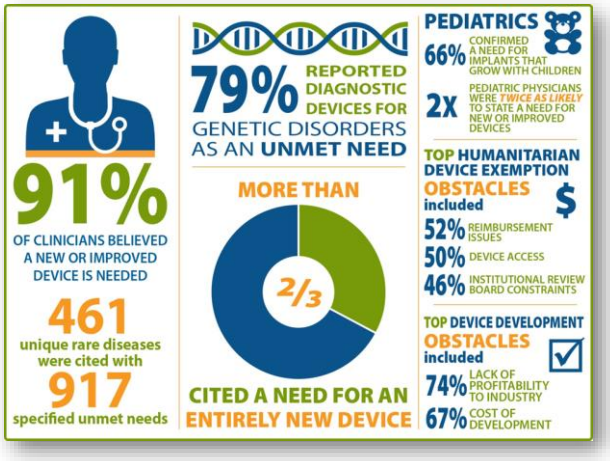
Stent implantations (99% off-label)

Balloon dilations (78% off-label)

Coil embolizations (29% off-label).

Sutherell JS, et al. Pediatric interventional cardiology in the United States is dependent on the off-label use of medical devices. Congenit Heart Dis. 2010 Jan-Feb;5(1):2-7. doi: 10.1111/j.1747-0803.2009.00364.x





Ref. https://www.fda.gov/industry/humanitarian-use-device-hud-designation-program/2018-fdancats-report-unmet-medical-device-needs-patients-rare-diseases

Examples of problems with off-label use from MHRA (2014)

Medical device and use	Problems caused
IV cannula / catheter used as arterial catheter	On removal, a section of the catheter was left in the patient.
A modular head and stem for a total hip replacement (not an approved combination)	Failure earlier than expected.
Single-use insulin needles were used more than once contrary to the manufacturer's instructions	Blockage and incorrect dosage reaching the patient.
A contact lens solution used during surgery rather than after surgery as stated in the instructions	Central toxic keratopathy.
A disposable temperature probe used via the nose rather than rectally / orally as stated in the instructions	Significant nose bleed.
A wheelchair modified to fit a docking system in a car	Damage to the wheelchair.
A defibrillator was unable to deliver a shock in manual or AED mode due to patient impedance being outside the specified range	Third-party electrodes used were not compatible with the defibrillator.
A user attempted to re-configure a Bain's breathing system	Breathing system did not work properly due to wrong size oxygen connector being put back into the system.
An IVD test was used for a sample type other than that recommended by the manufacturer	You should not perform IVD tests on samples other than those recommended by the manufacturer. If there is no alternative the laboratory performing the test will be responsible for these tests. They should have strong data to support the test on non-approved sample types.
An IVD test used with incorrect software	Incorrect results generated or delay to treatment and/or diagnosis.

https://www.gov.uk/government/publications/medical-devices-off-label-use/off-label-use-of-a-medical-device

What is the clinical perspective?

*… off-label use of medicinal products for rare disease patients has been compared to a double-edged sword; on the one hand it might be a **last resort** for patients in unique life-threatening situations, on the other hand, it also exposes them to **risks and experimentation***

Ref. Gupta SK, Nayak RP. Off-label use of medicine: perspective of physicians, patients, pharmaceutical companies and regulatory authorities. *J Pharmacol Pharmacother.* 2014;**5**:88–92. doi: 10.4103/0976-500X.130046

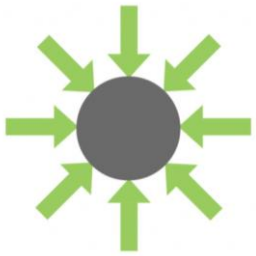
Necessary treatment versus experimentation?

What is known about the device and intervention generally?

What alternative treatment options are there?

What is known about off-label outcomes?

Will outcomes be reported, eg. case-report or registry?



What does MDR and guidance say?

MDR and IVDR

REGULATIONS

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure (2),

Whereas:

(1) Council Directive 90/385/EEC (3) and Council Directive 93/42/EEC (4) constitute the Union regulatory framework for medical devices, other than in vitro diagnostic medical devices. However, a fundamental revision of those Directives is needed to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures a high level of safety and health while supporting innovation.

(2) This Regulation aims to ensure the smooth functioning of the internal market as regards medical devices, taking as a basis a high level of protection of health for patients and users, and taking into account the small- and medium-sized enterprises that are active in this sector. At the same time, this Regulation sets high standards of quality and safety for medical devices in order to meet common safety concerns as regards such products. Both objectives are pursued simultaneously and are inseparably linked during the time they are in force. With regard to refer, to regard Article 114 of the Treaty on the Functioning of the European Union (TFEU), this Regulation harmonises the rules for the placing on the market and putting into service of medical devices and their accessories on the Union market thus allowing them to benefit from the principle of free movement of goods.

(1) Opinion of 14 February 2013 (OJ C 133, 9.5.2013, p. 52).
(2) Position of the European Parliament of 2 April 2014 (not yet published in the Official Journal) and position of the Council at first reading of 7 March 2017 (not yet published in the Official Journal).
(3) Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (OJ L 189, 20.7.1990, p. 17).
(4) Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (OJ L 169, 12.7.1993, p. 1).

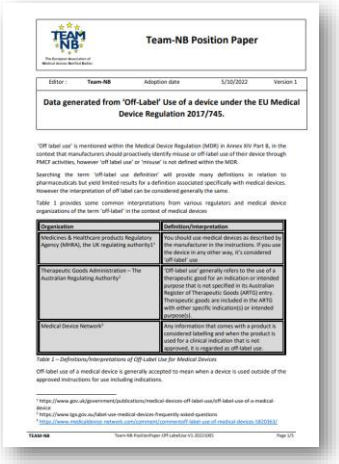
Annex XIV, part B

6.1. The PMCF plan shall specify the methods and procedures for proactively collecting and evaluating clinical data with the aim of:

…

(e) identifying possible **systematic misuse** or **off-label use** of the device, with a view to verifying that the intended purpose is correct.

TEAM-NB position paper from October 2022



Team-NB Position Paper

Editor : Team-NB | Adoption date 5/10/2022 | Version 1

Data generated from 'Off-Label' Use of a device under the EU Medical Device Regulation 2017/745.

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'Medical Device Network'[3]	Any information that comes with a product is considered labelling and when the product is used for a clinical indication that is not approved, it is regarded as off-label use.

Table 1 – Definitions/interpretations of Off-Label Use for Medical Devices

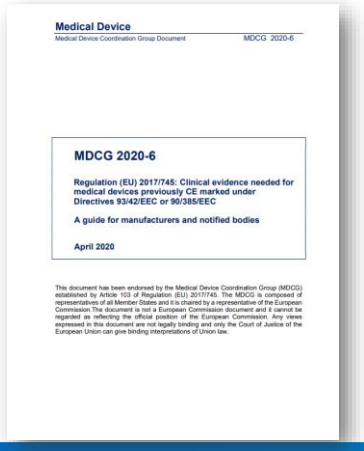
Off-label use of a medical device is generally accepted to mean when a device is used outside of the approved instructions for use including indications.

[1] https://www.gov.uk/government/publications/medical-devices-off-label-use/off-label-use-of-a-medical-device
[2] https://www.tga.gov.au/label-use-medical-devices-frequently-asked-questions
[3] https://www.medicaldevice-network.com/comment/comment-off-label-use-of-medical-devices-1402963/

TEAM-NB Team-NB Position Paper Off-Label Use V1 20221005 Page 1/5

Data from off-label use is clinical data

*Off-label data typically does not have 'sufficiency'. Whilst it may hold sufficient **quantity**, particularly if systematic off-label use has been identified, it however will often fail to have sufficient **quality** in terms or meaningful conclusions.*



Medical Device
Medical Device Coordination Group Document MDCG 2020-6

MDCG 2020-6

Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC

A guide for manufacturers and notified bodies

April 2020

This document has been endorsed by the Medical Device Coordination Group (MDCG) established by Article 103 of Regulation (EU) 2017/745. The MDCG is composed of representatives of all Member States and it is chaired by a representative of the European Commission.The document is not a European Commission document and it cannot be regarded as reflecting the official position of the European Commission. Any views expressed in this document are not legally binding and only the Court of Justice of the European Union can give binding interpretations of Union law.

Other pre-market data, e.g. case reports on experience with the use of the device in question, such as compassionate or humanitarian exceptional use reports. Note that this kind of pre-market data may be more prone to bias, compared to those listed above

MDCG 20206 continued…

9	Individual case reports on the subject device	This falls within the definition of clinical data under MDR Article 2(48), but is not considered a high quality source of data due to limitations in generalising findings to a wider patient population, reporting bias, etc. It may provide supportive or illustrative information with respect to specific claims.

MDCG 2020-7


Medical Device
Medical Device Coordination Group Document
MDCG 2020-7

MDCG 2020-7

Post-market clinical follow-up (PMCF) Plan Template
A guide for manufacturers and notified bodies

April 2020

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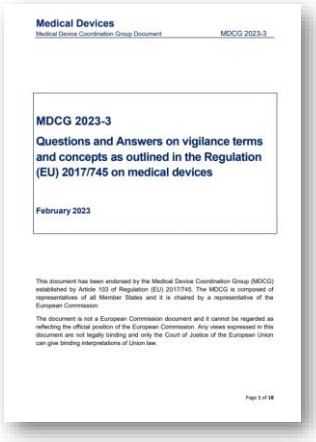
The aim of the PMCF plan is:

…

identifying possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct.

MDCG 2023-3


Medical Devices
Medical Device Coordination Group Document MDCG 2023-3

MDCG 2023-3
Questions and Answers on vigilance terms and concepts as outlined in the Regulation (EU) 2017/745 on medical devices

February 2023

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Page 1 of 18

'Abnormal use' is the **deliberate violation** of the intended use of a device. It is a **deliberate act or omission of an act** by the user that is counter to or **violates normal use** of a device, and is beyond any further reasonable means of interface-related risk control by the manufacturer.

An example of abnormal use may include off-label use of a device such as a doctor that, based on a medical decision, uses a device for a different indication than indicated in the manufacturer's instructions for use. Abnormal use of a device, must be documented and handled within the manufacturer's quality management system.

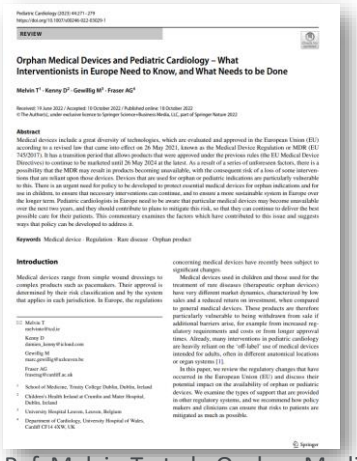
Why is policy challenging?

Regulatory reticence

Policy could open the floodgates

Number of aspects arguably fall outside ‘remit’
- patient care
- professional ethics
- development of research
- professional or product liability
- insurance
- reimbursement

MDR is changing market dynamics in Europe



Pediatric Cardiology (2023) 44:271–279
https://doi.org/10.1007/s00246-022-03029-1

REVIEW

Orphan Medical Devices and Pediatric Cardiology – What Interventionists in Europe Need to Know, and What Needs to be Done

Melvin T[1] · Kenny D[2] · Gewillig M[3] · Fraser AG[4]

Received: 19 June 2022 / Accepted: 10 October 2022 / Published online: 18 October 2022
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Abstract
Medical devices include a great diversity of technologies, which are evaluated and approved in the European Union (EU) according to a revised law that came into effect on 26 May 2021, known as the Medical Device Regulation or MDR (EU 745/2017). It has a transition period that allows products that were approved under the previous rules (the EU Medical Device Directives) to continue to be marketed until 26 May 2024 at the latest. As a result of a series of unforeseen factors, there is a possibility that the MDR may result in products becoming unavailable, with the consequent risk of a loss of some interventions that are reliant upon these devices. Devices that are used for orphan or pediatric indications are particularly vulnerable to this. There is an urgent need for policy to be developed to protect essential medical devices for orphan indications and for use in children, to ensure that necessary interventions can continue, and to ensure a more sustainable system in Europe over the longer term. Pediatric cardiologists in Europe need to be aware that particular medical devices may become unavailable over the next two years, and they should contribute to plans to mitigate this risk, so that they can continue to deliver the best possible care for their patients. This commentary examines the factors which have contributed to this issue and suggests ways that policy can be developed to address it.

Keywords Medical device · Regulation · Rare disease · Orphan product

Introduction

Medical devices range from simple wound dressings to complex products such as pacemakers. Their approval is determined by their risk classification and by the system that applies in each jurisdiction. In Europe, the regulations concerning medical devices have recently been subject to significant changes.

Medical devices used in children and those used for the treatment of rare diseases (therapeutic orphan devices) have very different market dynamics, characterized by low sales and a reduced return on investment, when compared to general medical devices. These products are therefore particularly vulnerable to being withdrawn from sale if additional barriers arise, for example from increased regulatory requirements and costs or from longer approval times. Already, many interventions in pediatric cardiology are heavily reliant on the 'off-label' use of medical devices intended for adults, often in different anatomical locations or organ systems [1].

In this paper, we review the regulatory changes that have occurred in the European Union (EU) and discuss their potential impact on the availability of orphan or pediatric devices. We examine the types of support that are provided in other regulatory systems, and we recommend how policy makers and clinicians can ensure that risks to patients are mitigated as much as possible.

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[4] Department of Cardiology, University Hospital of Wales, Cardiff CF14 4XW, UK

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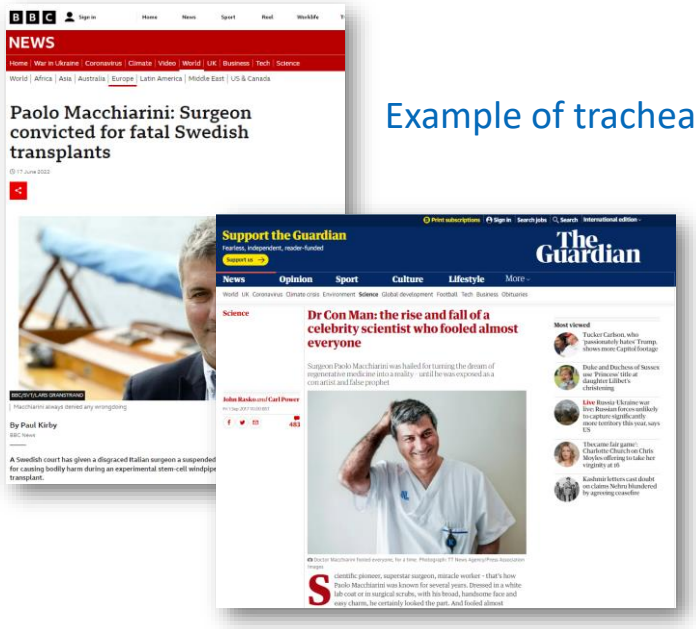
Time, cost, burden of assessment increasing

The effect of the transition timeline changes is TBD

Choice of devices typically used for ‘off-label’ purposes is becoming more limited

Ref. Melvin T et al., Orphan Medical Devices and Pediatric Cardiology - What Interventionists in Europe Need to Know, and What Needs to be Done. Pediatr Cardiol. 2023 Feb;44(2):271-279. doi: 10.1007/s00246-022-03029-1



Example of tracheal replacement

Together with his colleagues, Macchiarini carried out a total of eight such transplants between 2011 and 2014—three in Sweden and five in Russia.

The three patients in Sweden died and four of the five patients in Russia died.

https://doi.org/10.1136/bmj.o1516

What is needed, and what is happening?

What we need

Public health > technocratic focus

Better methodology for clinical evidence appraisal

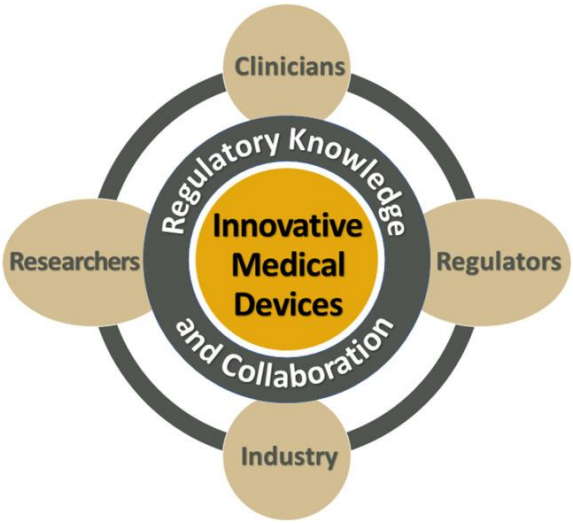
For essential devices – need to define / identify / protect with definitive policy

What is happening

MDCG taskforce on orphan / pediatric devices

Further legislation appears necessary

Forthcoming EU4health call on orphan / pediatric devices



Multi-disciplinary approach

Support essential interventions, stop unsafe ones and provide information when needed

Lottes AE, Navigating the Regulatory Pathway for Medical Devices-a Conversation with the FDA, Clinicians, Researchers, and Industry Experts. J Cardiovasc Transl Res. 2022 Oct;15(5):927-943.

CORE-MD
Coordinating Research and Evidence for Medical Devices

CORE-MD work packages on **hierarchy of evidence** and **paediatric** devices

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

IRDiRC working group on MedTech for rare disease

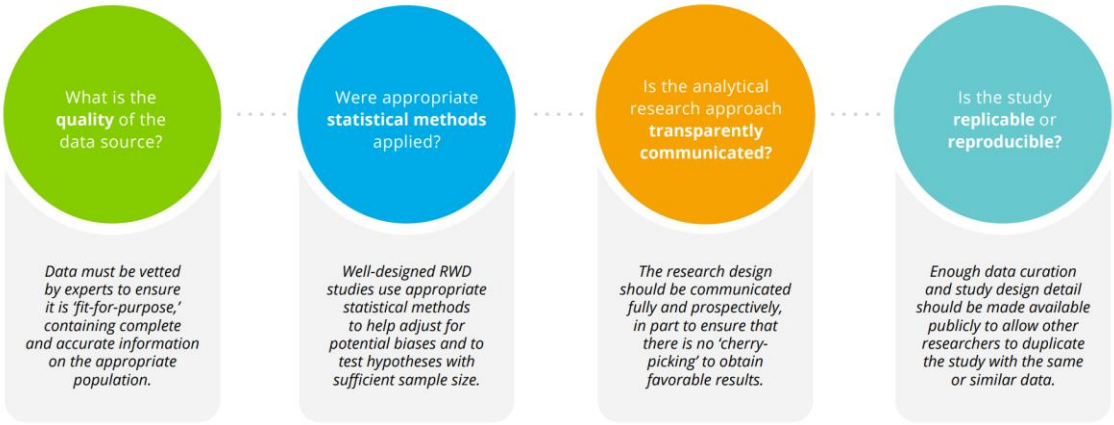
International experience

US FDA activities

PMDA market pathway for orphan drug / devices

Pediatric harmonisation by doing initiative

Focus on key questions



Ref. https://www.ispor.org/docs/default-source/strategic-initiatives/pfizer-bms-ispor-infographic_final.pdf?sfvrsn=a7413b04_0

With support, development is possible

frontiers in Pediatrics

Experience With Pediatric Medical Device Development

H. David Humes* and Angela J. Westrone

PEDIATRIC MEDICAL DEVICES: UNDERSERVED AND LARGELY IGNORED

This case study demonstrates that creative strategic planning, recognition of FDA pathways and support for pediatric devices can coalesce to promote the development of a life saving device reaching the bedside to save lives and save hospital costs with decreasing length of stays.

Ref. Humes D et al. Front. Pediatr., Volume 8 - 2020 https://doi.org/10.3389/fped.2020.00079

Ref. . Humes D et al. Front. Pediatr., Volume 8 – 2020 https://doi.org/10.3389/fped.2020.00079

The real-world context in which devices are used can be very different

The data requirements (real world or not) should not be

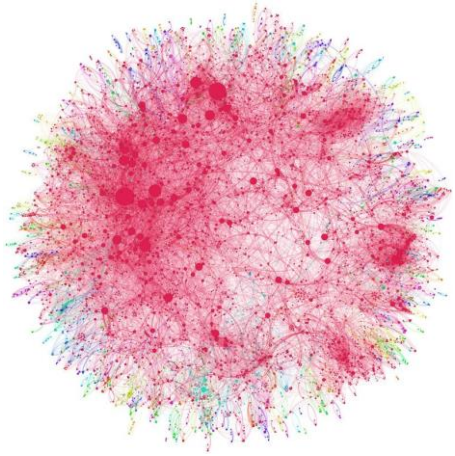


Image Ref. An Introduction to Complexity Theory

https://medium.com/@junp01/an-introduction-to-complexity-theory-3c20695725f8


Thank you