The Nordic Alliance for Clinical Genomics

IVDR Compliance Process

Cathrine H Nordhus & Courtney D Nadeau

Nordic Alliance
for Clinical Genomics

NACG week agenda

Please use ***#NACG2021*** for your social media

If you would like to join any additional sessions, please contact post@nordicclinicalgenomics.org

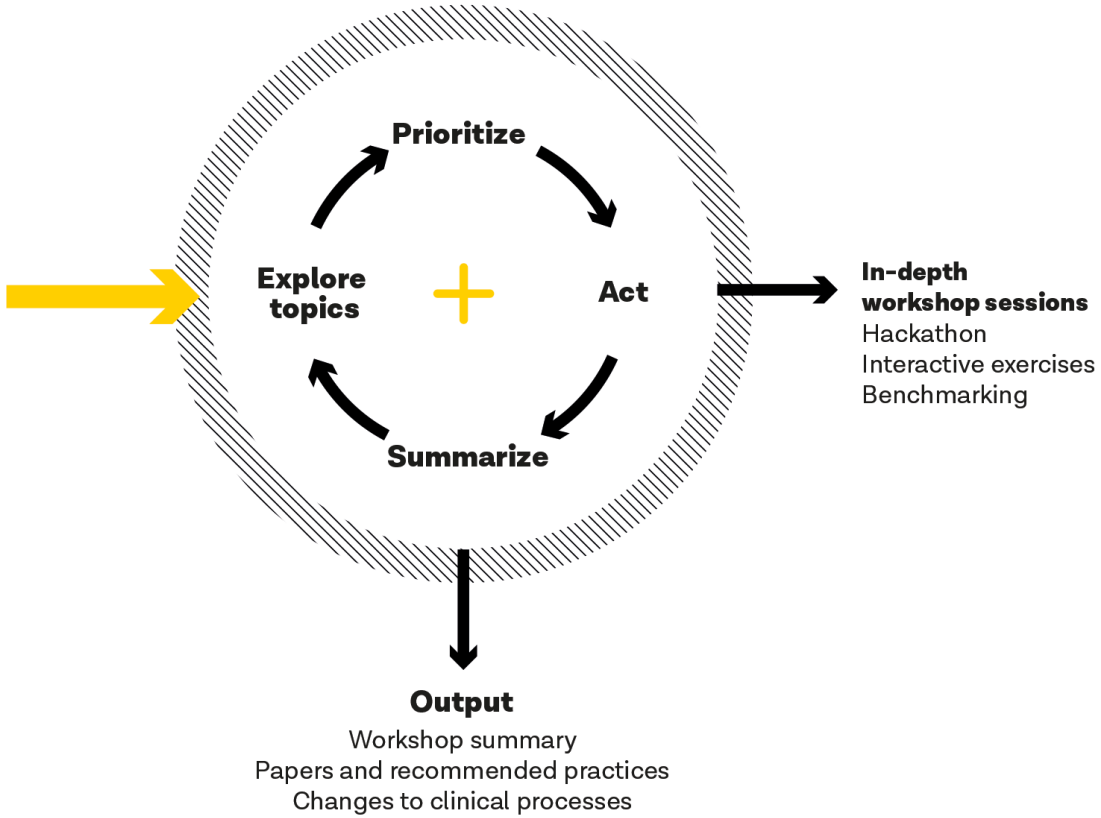
Time (Oslo GMT+2)	Monday 31st May	Tuesday 1st June	Wednesday 2nd June	Thursday 3rd June	Friday 4th June
12:00	**Opening and keynote** **Genome sequencing in clinical microbiology** Rasmus L Marvig, Center for Genomic Medicine, Rigshospitalet DK	**Digital dynamic consent in clinical genomics** Sharmini Alagaratnam, and Courtney Nadeau, DNV NO	**Somatic variant calling - benchmarking exercise with in-silico spiked-in variants.** Oleg Agafonov, DNV NO, Valtteri Wirta, Clinical Genomics Stockholm, SciLifeLab SE	**Variant interpretation and data sharing** Dag Undlien, OUS NO; Stephen McAdam, DNV NO; and Sharmini Alagaratnam DNV NO	**Clinical diagnostic unsolved cases** Maria Rossing, Center for Genomic Medicine, Centre of Diagnostic Investigations, Rigshospitalet DK
12:30					
13:00	**Automation of sequencing operations and data management** Tony Håndstad, Department of Medical Genetics, OUS NO	**IVDR compliance progress** Cathrine Høgseth Nordhus, Department of Medical Genetics, OUS NO			**Social networking hour** Sharmini Alagaratnam, DNV NO
13:30			END		
14:00	END	END		END	END

The Nordic Alliance for Clinical Genomics – NACG

- an independent association open for organizational and individual members

NACG brings together leading stakeholders in clinical genomics across the Nordics.

- **Mission:**
  - We work together and learn from each other to lift our performance standards.
  - We aim at responsible sharing of trustworthy data for improved diagnosis and treatment, and as a resource for research.
- **How we work:**
  - Practical collaboration through interactive cross-disciplinary workshops and projects.



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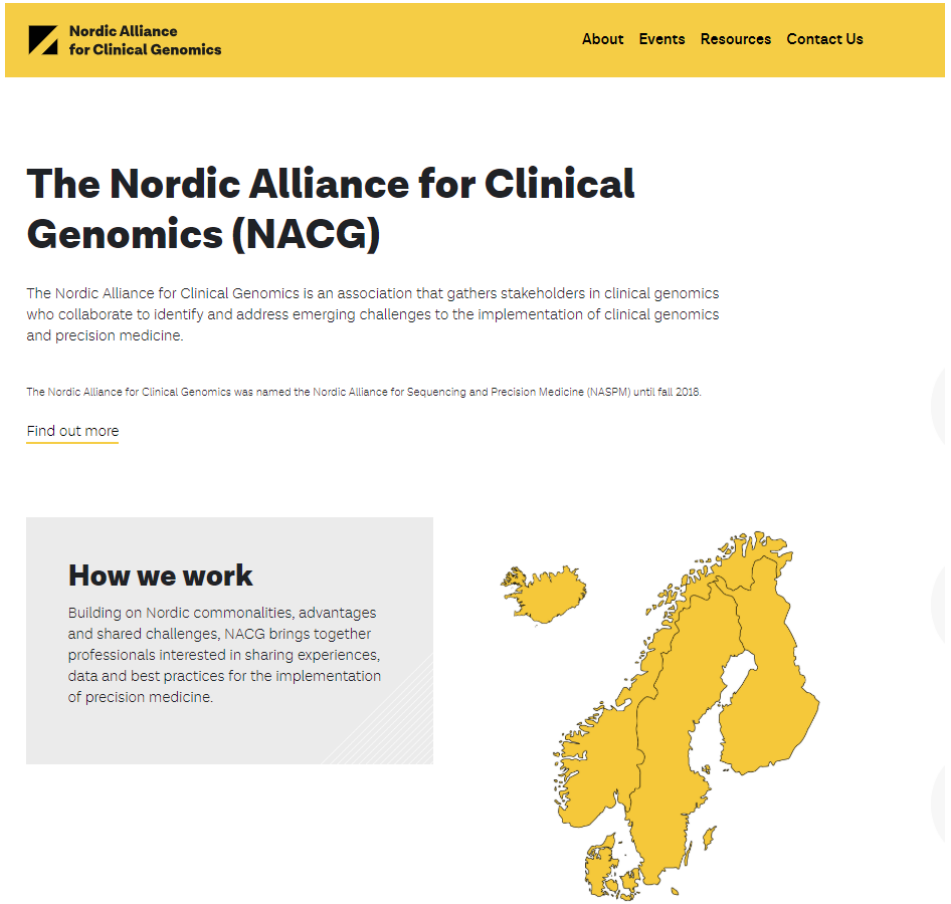


- **NACG website**
  - https://nordicclinicalgenomics.org/
  - Resources
    - NACG paper
    - NACG workshop reports
    - NACG governing documents
  - How to apply for membership
    - Organisations
    - Individuals
- **Contact us**
  - post@nordicclinicalgenomics.org

NACG - zoom meeting guidelines

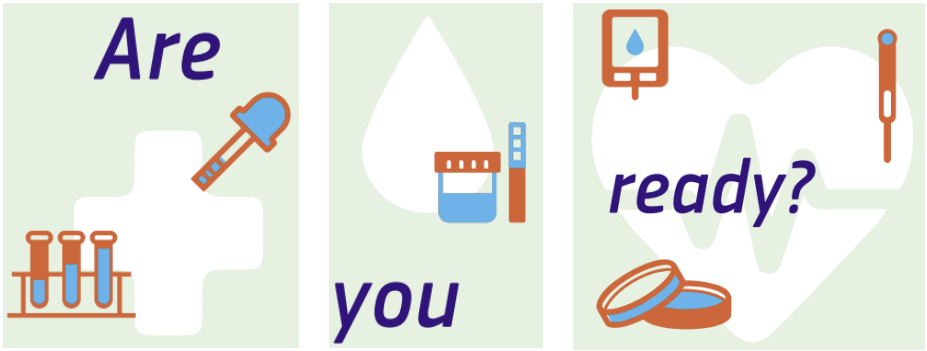
- Attendees are muted by default due to the size of the groups – please stay this way unless feedback is requested
- Please post questions in the chat
- The workshop will be documented in a NACG report – to be published at https://nordicclinicalgenomics.org/
- Sessions are recorded to help in report production
- Please inform if anything should be kept out of the report.

IVDR

at

10th NACG Workshop

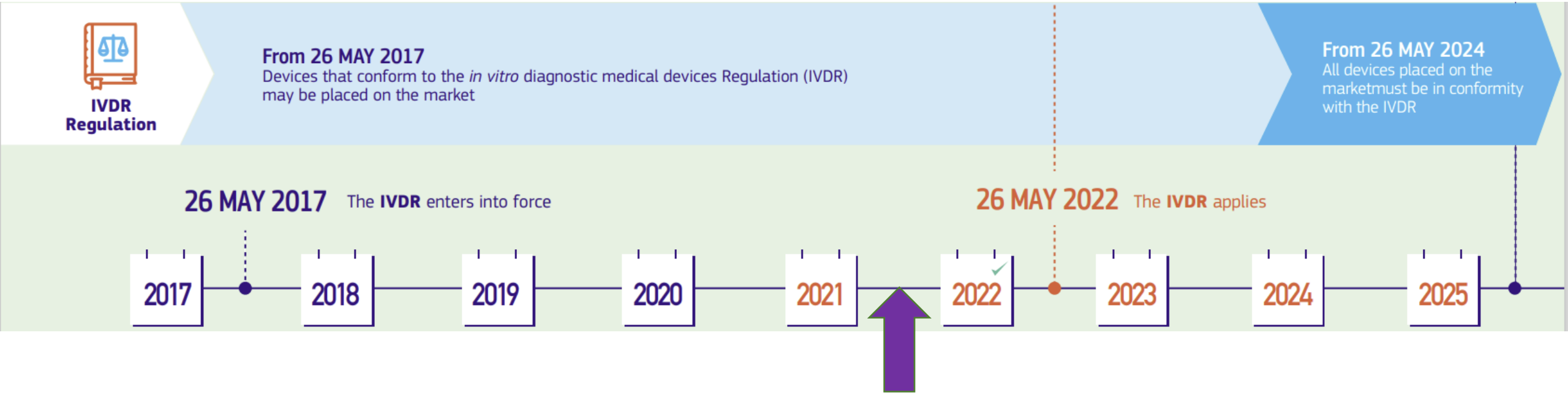
by Cathrine Nordhus



Agenda

1. IVDR – short recap from previous NACG workshops
2. Status of IVDR compliance process at OUS and in Norway
3. Market Surveillance and Self Declaration– proposed processes at OUS
4. Status of EU guidance documents and endorsed documents
5. Guidance on in-house requirements (for Northern Ireland)
6. Qualification and Classification of Medical Device Software (MDSW)
7. Status of Notified Body process at DNV
8. Artificial Intelligence Act (quick mention)

IVDR Timeline

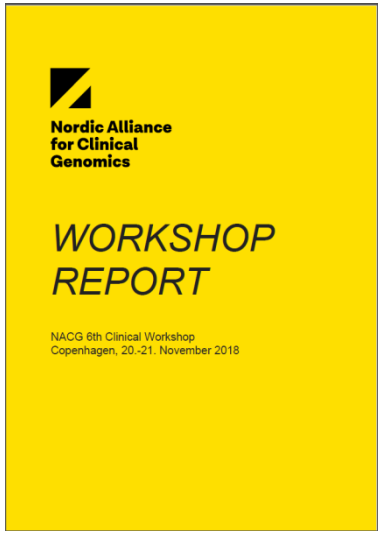


< 1 year to go

Background – IVDR at NACG meetings

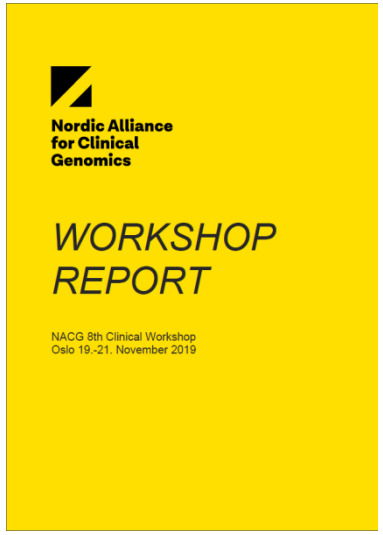
Copenhagen, November 2018

Courtney Nadeau, DNV GL, introduced the IVDR which replaces previous IVD directive 98/79/EC and takes primacy over national law



Oslo, November 2019

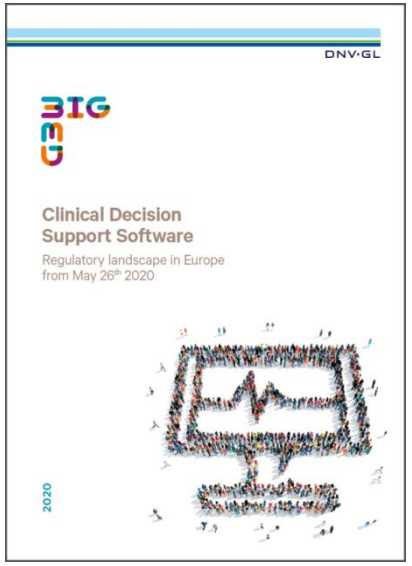
Alexey Shiryaev and Nick Baker, both from DNV GL Presafe AS, provided an overview of the MDR and IVDR, discussed applicability and requirements for transition.



Webinar, November 2020

Cathrine Nordhus, OUS, presented status of work in Norway and with a goal to establish working groups that will collaborate across the Nordic region

IVDR related white papers available through Big Med Project



Status IVDR compliance process at OUS

IVDR collaboration in Norway

National (Clinic for Laboratory Medicine):

- Collaboration between university hospitals in Norway at clinic level:
  - Oslo University Hospital
  - Haukeland University Hospital
  - St Olav University Hospital
  - Universitetssykehuset Nord-Norge
- Goal of aligning the efforts to secure IVDR compliance in all regions and across laboratory disciplines.

National (Department of Medical Genetics):

- Starting up medical genetics department collaboration between:
  - Oslo
  - Skien
  - Trondheim
  - Tromsø
- Goal is to share the work load and to align activities to secure compliance.

IVDR in Health Region South East

Communication with competent authority	Mapping and classification of IVDs	Procedures for IVDR compliance
• No guidelines for the interpretation of the new regulation have been provided in Norway • Various stakeholders have provided input during the consultation process for the new regulation • Request for clarification has been sent to Legemiddelverket from the IVDR project team in HSØ. • There is still very little guidance from the Norwegian Medicines Agency	• Mapping of IVDs in use and classification* is underway in all work groups • Market surveillance has started in some work groups. ***All genetics tests are class C IVDs**	• Guidance document for IVDR • Draft procedure for Market Surveillance, incl. templates • Procedure for self declaration of inhouse IVDs, including templates

IVDR at Oslo University Hospital

Activities

- Mapping of all laboratory developed tests in all laboratory diagnostic departments is underway
- Determine further course of action for all IVDs (following market surveillance for commercial alternatives):
  - A. Continue In-house approach?
  - B. CE-mark?
  - C. Change to commercial alternative?
- Implement plan to secure compliance
  - A. Prepare self declaration forms for all In-house devices
  - B. Prepare necessary documentation to start CE-marking process with notified body (if applicable)
  - C. Procure CE-marked kits and implement in lab

Deliverables:

- Overview of all current IVDs (in-house and commercial) per department
- Establish plan to secure IVDR compliance per department
- Documentation of Market Surveillance activities including comparison of available commercial alternatives for all IVDs
- Self Declaration forms for In-house IVDs
- If applicable, prepare necessary documentation to start CE marking process for IVDs.

IVDR at OUS – Evaluation of Equivalent Commercial IVDs

Laboratory developed tests can only be used if there are no equivalent commercial IVDs available.

As part of the work to map the different in-house IVDs all health institutions will have to monitor the market for commercial alternatives.

Relevant sources for this can be:

- Product catalogues from suppliers of IVD equipment
- Search engines
- EUDAMED (when available 2022)
- External quality programs

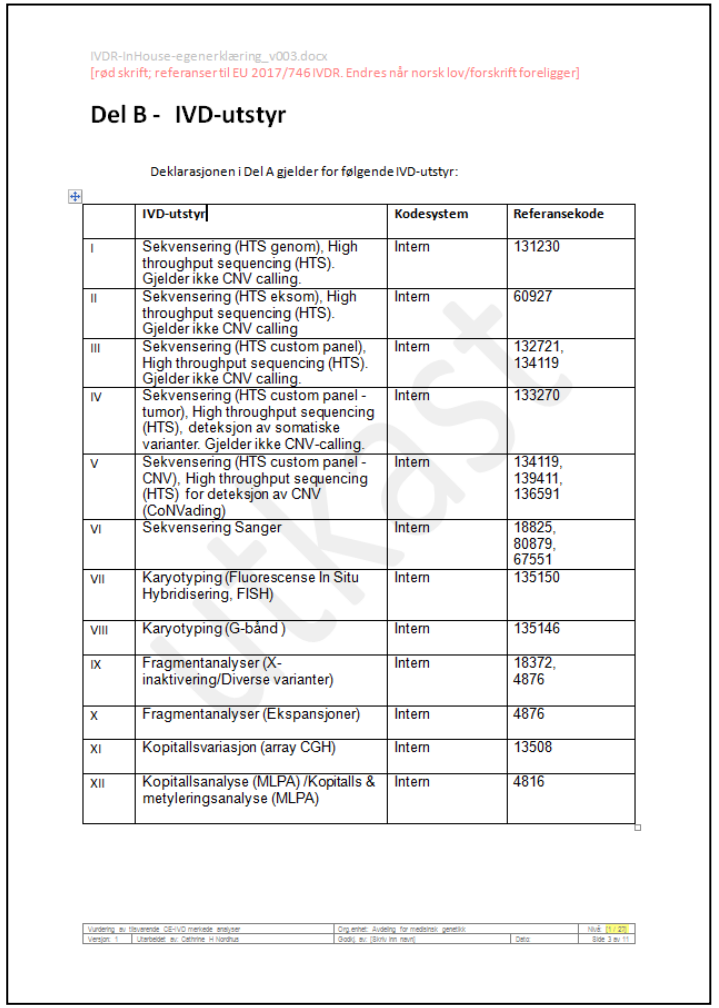
OUS plans to do this when mapping all IVDs and determining which IVDs should remain inhouse, when developing new IVDs in the laboratory, and then every third year when IVD is in use.

OUS has proposed a list of 11 different criteria to be used when comparing IVDs:

	Criteria	Yes/No/ Not relevant	If no or not relevant please elaborate
1	Is the analyte / reference material identical?		
2	Is the intended purpose of the devices the same?		
3	Is the sample material used by the IVD the same?		
4	Are reporting units the same?		
5	Is the analysis principle the same?		
6	Is analytical performance the same?		
7	Is capacity and degree of automation sufficient?		
8	Does the test require the same equipment/products?		
9	Is the concentration/measurement area the same?		
10	Is the alternative IVD CE-IVD marked and available on the market?		
11	Does the alternative IVD correspond to the in-house IVD with regards to other criteria not listed above?		
	Is the proposed IVD equivalent? (all criteria are fulfilled or not relevant)		

IVDR at OUS – Approach to Self Declaration

- The department of medical genetics is accredited to ISO 15189, and in discussions within the work group in Health Region South East the medical genetics work group the medical genetics lab at OUS has decided to set up the initial self declaration document based on the accreditation scope (Part B of the self declaration)
- The various method descriptions are more or less identical, e.g. for the NGS methods it is only the panel filtering criteria that differs from panel to panel.
- We have established an excel template where we record compliance with each general safety and performance requirement for every method.
- If later, we decide that we have to prepare one declaration per method, it will be easy to expand the excel spreadsheet with one row per panel, including specific details on indication per panel under intended use, and adding details on the list of genes for each panel in the "Electronically programmable systems" column in part C of the Self Declaration



IVDR-InHouse-egenerklæring_v003.docx
[rød skrift; referanser til EU 2017/746 IVDR. Endres når norsk lov/forskrift foreligger]

Del B - IVD-utstyr

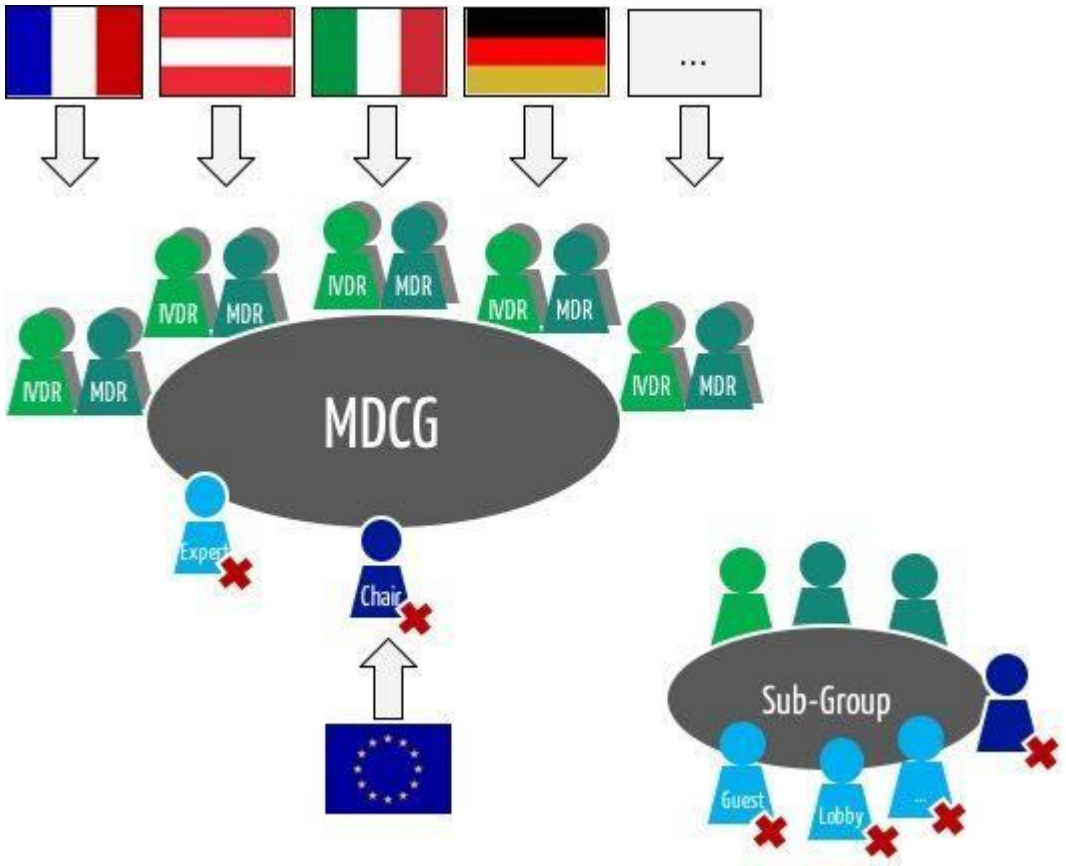
Deklarasjonen i Del A gjelder for følgende IVD-utstyr:

	IVD-utstyr	Kodesystem	Referansekode
I	Sekvensering (HTS genom), High throughput sequencing (HTS). Gjelder ikke CNV calling.	Intern	131230
II	Sekvensering (HTS eksom), High throughput sequencing (HTS). Gjelder ikke CNV calling	Intern	60927
III	Sekvensering (HTS custom panel), High throughput sequencing (HTS). Gjelder ikke CNV calling.	Intern	132721, 134119
IV	Sekvensering (HTS custom panel - tumor), High throughput sequencing (HTS), deteksjon av somatiske varianter. Gjelder ikke CNV-calling.	Intern	133270
V	Sekvensering (HTS custom panel - CNV), High throughput sequencing (HTS) for deteksjon av CNV (CoNVading)	Intern	134119, 139411, 136591
VI	Sekvensering Sanger	Intern	18825, 80879, 67551
VII	Karyotyping (Fluorescense In Situ Hybridisering, FISH)	Intern	135150
VIII	Karyotyping (G-bånd)	Intern	135146
IX	Fragmentanalyser (X-inaktivering/Diverse varianter)	Intern	18372, 4876
X	Fragmentanalyser (Ekspansjoner)	Intern	4876
XI	Kopitallsvariasjon (array CGH)	Intern	13508
XII	Kopitallsanalyse (MLPA) /Kopitalls & metyleringsanalyse (MLPA)	Intern	4816

Oslo University Hospital

Guidance Documents for IVDR

from the
Medical Devices Coordination Group (MDCG)



EU Guidance Documents – in progress

Scope	Group Deliverables	Consult prior to MDCG	Planned MDCG endorsement	Additional Comments
5. Market Surveillance Documents				
MDR + IVDR	*Update of PRRC Guidance*	TBD	2021	
MDR + IVDR	*Authorised Representatives*	TBD	2021	
MDR + IVDR	*In-house manufacturers*	IVD	2021	
MDR + IVDR	*Guidelines on Re-labelling & Re-packaging*	NBO	2021	
MDR	*Q&A on Custom-Made & Adaptable Devices*	N/A	2021	Now under Ad-hoc Task Force of MDCG
MDR + IVDR	*Q&A on Importers & Distributors*	TBD	2021	
MDR + IVDR	*Update of PRRC Guidance*	TBD	2021	
11. Guidance documents related to In Vitro Diagnostic Medical Devices (IVD)				
IVDR	Performance evaluation	CIE	2021	Comments received as part of stakeholder consultation
IVDR	SSP (Summary of Safety & Performance) template and guidance	CIE	2021	
IVDR	Development of common specifications for SARS-CoV-2, to be published as guidance in the interim	N/A	2021	Draft under revision
IVDR	Qualification of assays used in clinical trials of medicinal products	N/A	2021	In collaboration with competent authorities for medicinal products
IVDR	In-house Devices	MS	2021	Joint with Market Surveillance MDCG sub-group, discussion ongoing
IVDD	Notice to manufacturers on the impact of genetic variants	N/A	2021	Stakeholder consultation being launched

https://ec.europa.eu/health/sites/health/files/md_sector/docs/mdcg_ongoing_guidancedocs_en.pdf

MDCG endorsed documents

IVDR

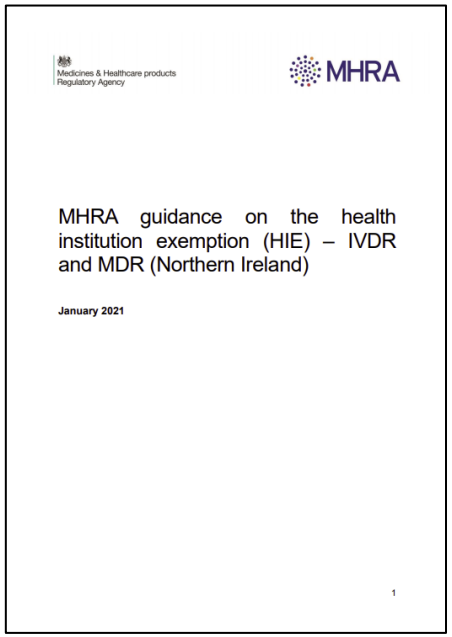
Reference	Title	Publication
MDCG 2021-4	Application of transitional provisions for certification of class D in vitro diagnostic medical devices according to Regulation (EU) 2017/746	April 2021
MDCG 2020-16	Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746	November 2020

New technologies (MDSW)

Reference	Title	Publication
Infographic	Is your software a Medical Device?	March 2021
MDCG 2020-1	Guidance on clinical evaluation (MDR) / Performance evaluation (IVDR) of medical device software	March 2020
MDCG 2019-16 rev.1	Guidance on cybersecurity for medical devices	December 2019
MDCG 2019-11	Qualification and classification of software - Regulation (EU) 2017/745 and Regulation (EU) 2017/746	October 2019

https://www.medical-device-regulation.eu/mdcg-endorsed-documents/

Guidance on Health Institution Exemption (Northern Ireland)


Medicines & Healthcare products Regulatory Agency

MHRA

MHRA guidance on the health institution exemption (HIE) – IVDR and MDR (Northern Ireland)

January 2021

1

Health_institution_exemption.pdf (publishing.service.gov.uk)

Justification for using In-House IVD

The health institution's justification for applying the exemption must be that the target patient group's specific needs cannot be met or cannot be met at the appropriate level of performance by an equivalent device available on the market. The justification should include evidence (e.g. market surveys/literature reviews) for the availability on the market of equivalent CE marked or CE UKNI marked devices

Critical features might include:

- patient needs
- device functionality
- device performance
- device reliability
- result turn-around times or order lead time
- systems compatibility

Research use products with no device CE mark

Health institutions who procure or repurpose products labelled for 'research-use' or otherwise products that are not CE marked or CE UKNI marked as devices, and then use the product for patient management or in a manner that may influence patient care decisions will need to **apply the requirements of the exemption.**

Transfer of devices between legal entities

A transfer refers to any type of legal transfer including a loan or gift. To transfer a device between health institutions **each health institution will need to apply the exemption separately** with each applying the requirements of the exemption including making a separate declaration.

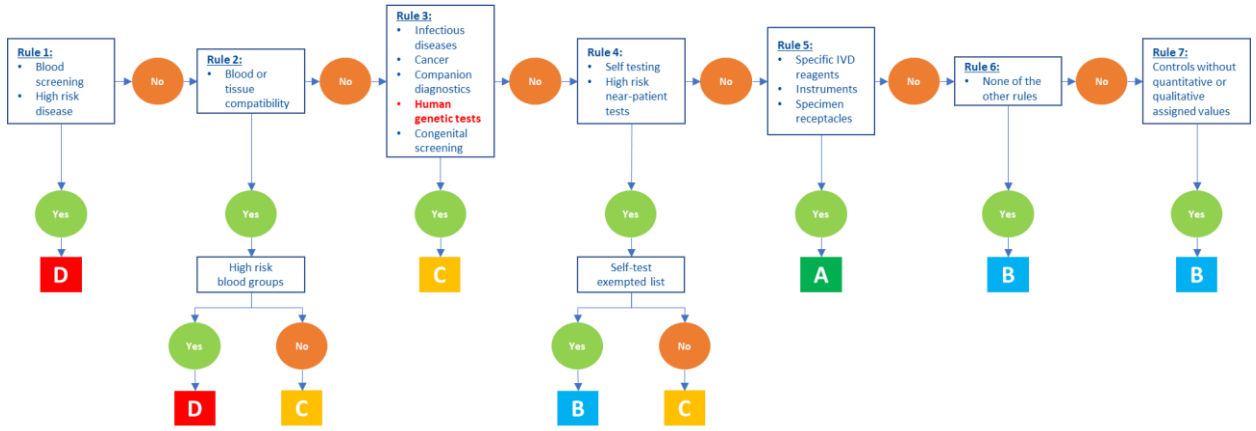
Documentation sharing between original and transfer health institutions will facilitate this process

Use of open source software

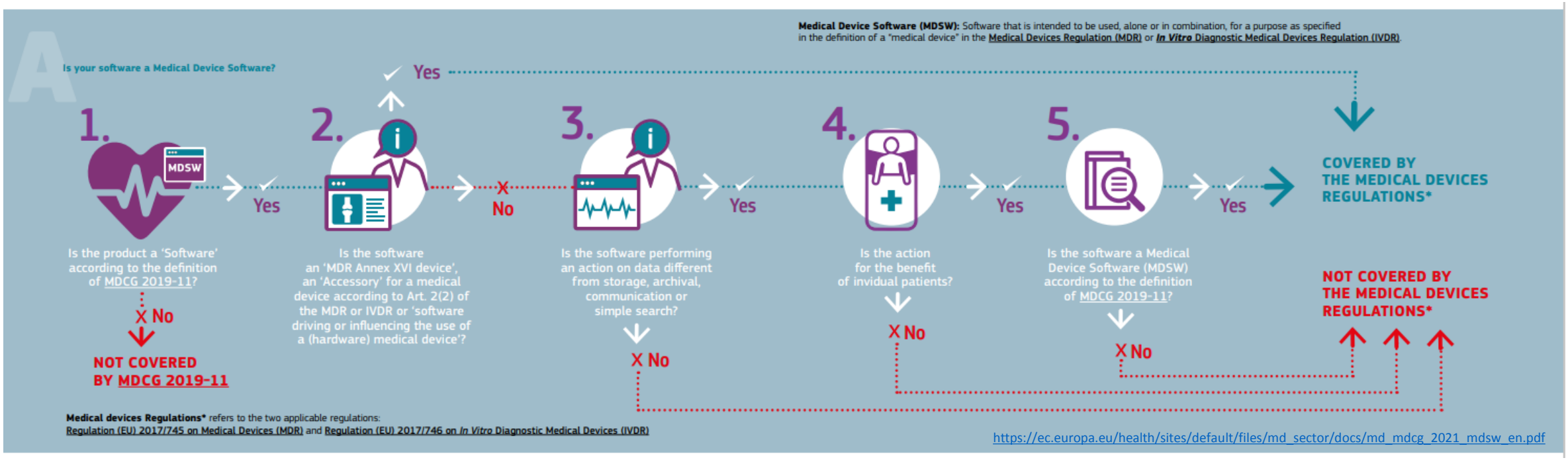
When manufacturing or modifying and using devices with open-source or cloud-based components (including software and hardware), health institutions need to have, as part of their quality management system, sufficient responsibility and control throughout the lifetime of the device.

The health institution should consider whether they have **sufficient information about the safety, quality and performance of the componen**t to meet the relevant requirements of Annex I in the IVDR/MDR.

Qualification and Classification of Medical Device Software (MDSW)



Does the Medical Device Regulations apply?



https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2021_mdsw_en.pdf

MEDICAL DEVICES REGULATIONS:

Refers to the two applicable regulations:

- Regulation (EU) 2017/745 on Medical Devices (MDR)
- Regulation (EU) 2017/746 on In Vitro Diagnostic Medical Devices (IVDR)

MEDICAL DEVICE SOFTWARE (MDSW)

Medical device software is software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a “medical device” in the medical devices regulation or in vitro diagnostic medical devices regulation.

https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2021_mdsw_en.pdf

Medical Device Software covered by IVDR

MDSW which provides information according to Regulation (EU) 2017/746 – IVDR Article 2(2) (a) to (f) should qualify as In Vitro Diagnostic Medical Device Software (IVD MDSW)

a) concerning a physiological or pathological process or state (by investigation of this process or state); or

b) concerning congenital physical or mental impairments

c) concerning the predisposition to a medical condition or a disease;

d) to determine the safety and compatibility with potential recipients;

e) to predict treatment response or reactions;

f) to define or monitoring therapeutic measures.

Medical Device Software covered by MDR

A MDSW which falls under the definition set out in EU Article 2 (1) of Regulation (EU) 2017/745 – MDR should qualify as Medical Device Software (MD MDSW).

In specific, the following considerations should apply on the provision of information by software on:

g) diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease

h) diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,

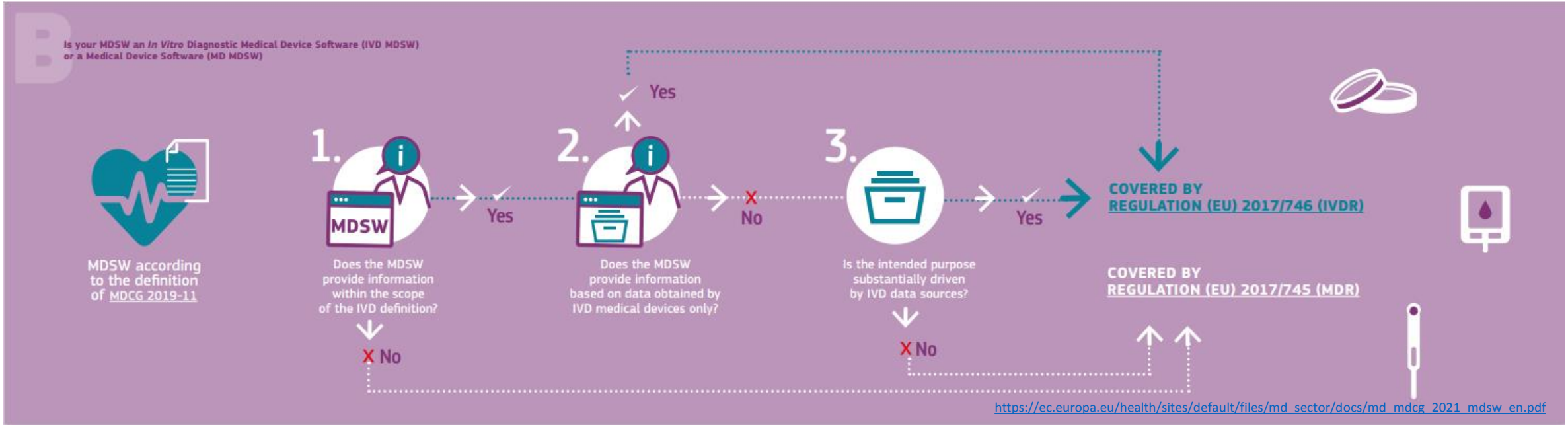
i) investigation, replacement or modification of the anatomy or of a physiological or

j) pathological process or state, control or support of conception;

k) products specifically intended for the cleaning, disinfection or sterilization of devices as

referred to in Article 1(4) and Annex XVI products

Is your software a MD or an IVD?



(MDSW) Medical device software definition

Medical device software is software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a "medical device" in the medical devices regulation or in vitro diagnostic medical devices regulation.

Does the MDSW provide information within scope of IVD definition?

MDSW which provides information according to Regulation (EU) 2017/746 – IVDR Article 2(2) (a) to (f) should qualify as In Vitro Diagnostic Medical Device Software (IVD MDSW):

a) concerning a physiological or pathological process or state (by investigation of this process or state); or
b) concerning congenital physical or mental impairments
c) concerning the predisposition to a medical condition or a disease;
d) to determine the safety and compatibility with potential recipients;
e) to predict treatment response or reactions;
f) to define or monitoring therapeutic measures.

MDSW Qualification Example – Bioinformatics pipeline

Example 4:

- A bioinformatics MDSW intended to analyse digital Next Generation Sequencing (NGS) raw data coming from sequenced patient's cancer genomes.
- It allows the detection and visualisation of somatic genome alterations (such as substitutions, small insertions and deletions (indels), copy number alterations, and genomic rearrangements) across a selected number of genes.
- Additionally, it is also capable of determining genomic signatures* (such as microsatellite instability [MSI] and/or tumour mutational burden [TMB]).
- The types of somatic genome alterations and genomic signatures detected depend on the test chosen.
- The MDSW assists the user in identifying and visualising genomic alterations and is intended to identify somatic genome alterations to support diagnosis and treatment decisions.

Qualification:

- Decision step 1 is concluded with a "yes" as the **MDSW is intended for analysing congenital data to provide information on the predisposition to a medical condition or disease**, thus meeting criteria (b) and (c) laid out in the decision step.
- As the **MDSW processes data coming only from in vitro diagnostic medical devices into the calculation**, then the software is qualified as an IVD MDSW according to Step 2.

https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2019_11_guidance_qualification_classification_software_en.pdf

MDSW Qualification Example – Combined test (Prenatal screening)

Example 3:

- A MDSW algorithm intended to provide information on the statistical predisposition for Down syndrome (Trisomy 21) and Edwards syndrome (Trisomy 18) in the first and second trimesters of pregnancy.
- The MDSW analyses input data from various in vitro diagnostic medical device assays as well as, ultrasound measurements of the nasal bone or neck fold.
- The MDSW provides clinicians/obstetricians with a risk factor score for a foetus's likelihood of having genetic mutations in the first or second trimester of pregnancy. The risk score suggests whether or not additional diagnostic testing is needed to confirm the genetic mutations of Trisomy 21, Trisomy 18.

Qualification:

- Decision Step 1 can be answered "yes" as the **software bears a medical purpose and fulfils the definition of MDSW**. The MDSW meets criteria (c) as it provides information according to the in vitro diagnostic medical devices definition.
- Decision Step 2 is answered "no" as an imaging measurement is included in the calculation.
- Decision Step 3 is answered "yes" as the intended purpose is **substantially driven by in vitro diagnostic medical device data** resulting in the qualification of the software as an IVD MDSW (**as the data received from the in vitro diagnostic medical devices (markers) are deemed decisive for the overall calculation result (output) achieved by the MDSW**).

https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2019_11_guidance_qualification_classification_software_en.pdf

Classification of Medical Device Software (MDSW)

The classification rules for IVDs is defined in Annex VIII of the regulation. This also applies when classifying medical device software (MDSW):

Application of the classification rules shall be governed by the intended purpose of the devices:

Classification rule 3i "Devices are classified as class C if they are intended for human genetic testing" also applies to our bioinformatic pipelines for genetic testing

Document MDCG 2019/11 highlights rule 1.4 and 1.9 of the annex:

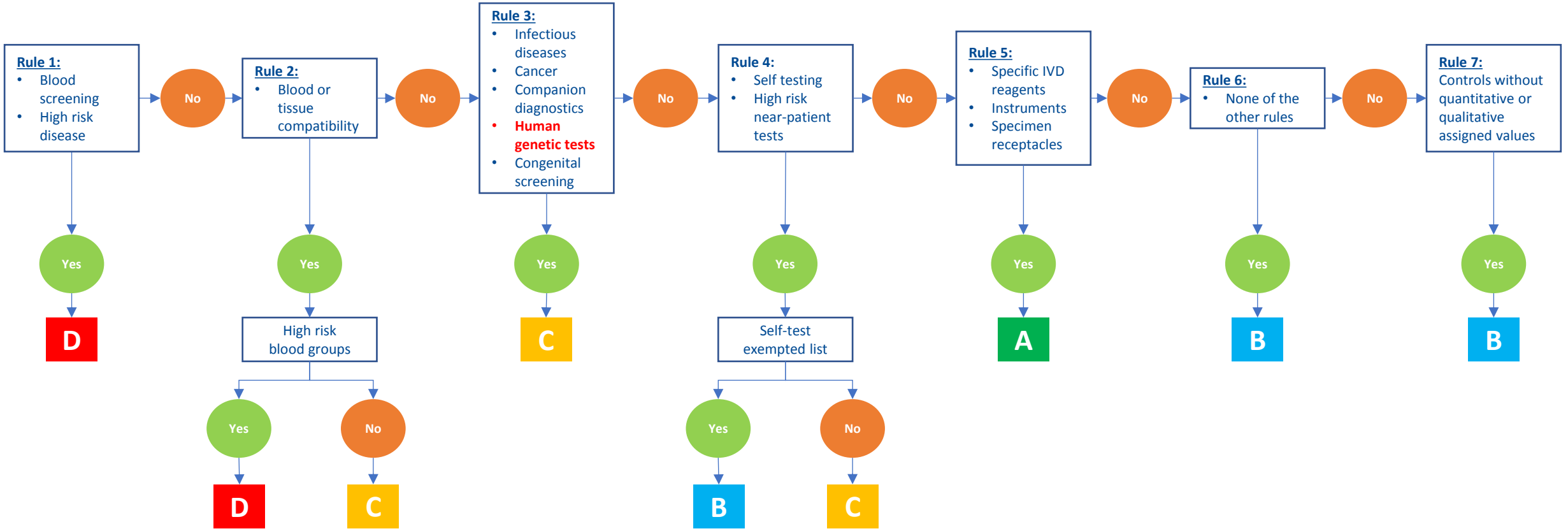
1.4 Software, which drives a device or influences the use of a device, shall fall within the same class as the device. If the software is independent of any other device, it shall be classified in its own right.

1.9 If several classification rules apply to the same device, the rule resulting in the higher classification shall apply

https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2019_11_guidance_qualification_classification_software_en.pdf
https://eur-lex.europa.eu/eli/reg/2017/746/oj

Classification of Medical Device Software (MDSW) per IVDR

The 7 classification rules for IVDs is defined in Annex VIII of the IVDR. This also applies when classifying medical device software (MDSW):



WHEN TRUST MATTERS

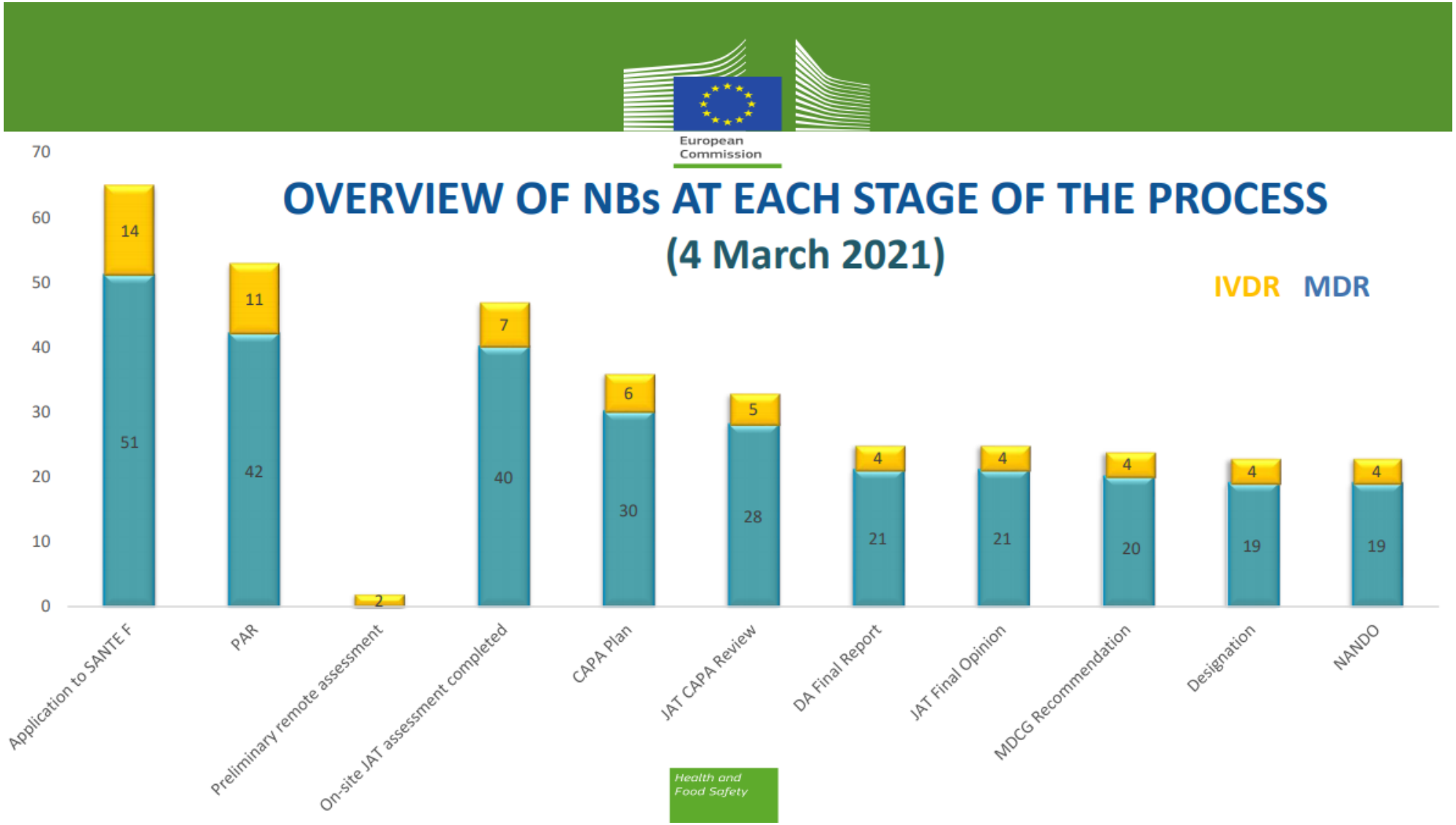
NACG: Regulatory Update

Group Research and Development: Healthcare

Courtney Nadeau

Update on EU MDR and IVDR Notified Bodies

Notified Body Status as of Q1 2021



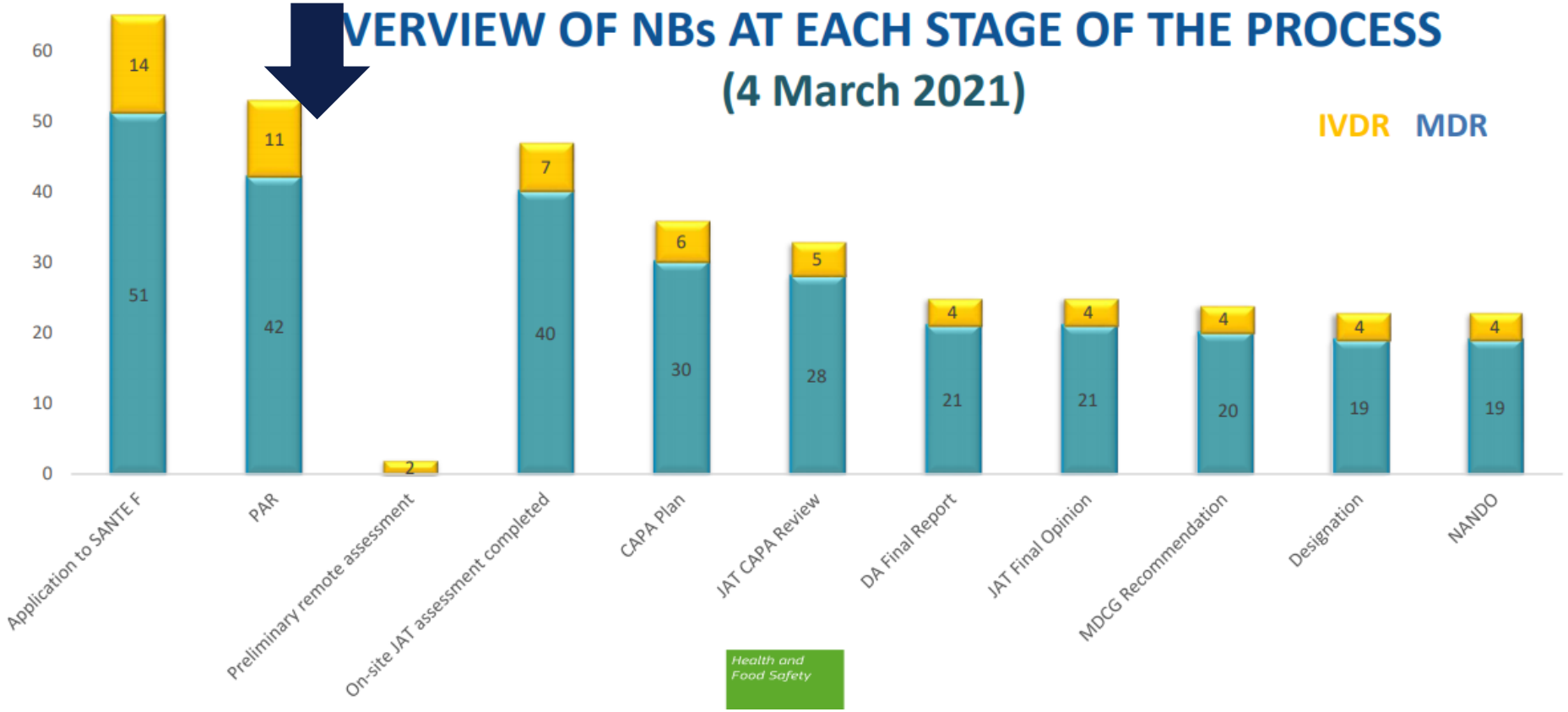
How to find a Notified Body (NANDO)

https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=35

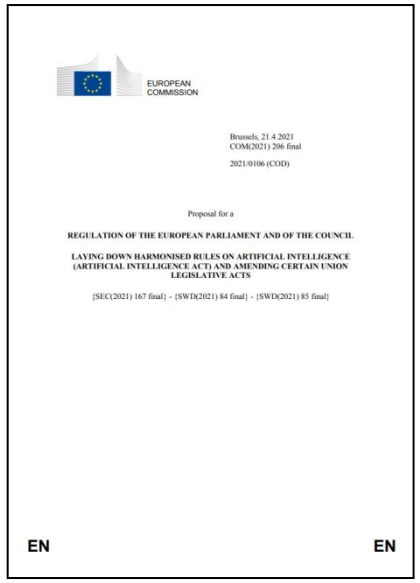
- Scope of Notified Bodies (NBOG Codes)
  - **IVR Codes:** Codes reflecting design and intended purpose (ie. IVR0402: devices intended to be used to predict genetic disease/disorder risk and prognosis)
  - **IVS Codes:** IVDs with specific characteristics (ie. IVS1003: devices intended to be used as companion diagnostics)
  - **IVT Codes**: IVD using specific technologies (ie. IVT2006:devices manufactured using chemical processing)
  - **IVP Codes:** IVD which require specific knowledge for examination (ie. IVP3006:devices requiring knowledge regarding flow cytometry)
  - **IVD Codes:** IVD which require specific knowledge in lab/clinical disciplines (ie. IVD4012:devices which require knowledge regarding virology)

DNV as IVDR NB

- Applied for full scope (all codes, all devices)
- Currently undergoing preliminary assessment



Proposed Artificial Intelligence Regulation



EUROPEAN COMMISSION

Brussels, 21.4.2021
COM(2021) 206 final
2021/0106 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

LAYING DOWN HARMONISED RULES ON ARTIFICIAL INTELLIGENCE (ARTIFICIAL INTELLIGENCE ACT) AND AMENDING CERTAIN UNION LEGISLATIVE ACTS

{SEC(2021) 167 final} - {SWD(2021) 84 final} - {SWD(2021) 85 final}

EN EN

https://ec.europa.eu/newsroom/dae/redirection/document/75788

- To promote the development of AI and address the potential high risks it poses to safety and fundamental rights equally, the European Commission is presenting both a proposal for a regulatory framework on AI and a revised coordinated plan on AI.
- The Commission is proposing new risk based rules to make sure that AI systems used in the EU are safe, transparent, ethical, unbiased and under human control.

NACG – for you, by you!

- Where should NACG focus next?
- Give your input through
  - Post NACG-week survey
  - post@nordicclinicalgenomics.org

16/08/2021

Nordic Alliance
for Clinical Genomics