Guidance Document for Consistent Reporting of 'Omics Data From Various Sources

- Transcriptomics Reporting Framework (TRF)
- Metabolomics Reporting Framework (MRF)

Joshua Harrill (US EPA) and Mark Viant (Univ. Birmingham, UK)

WPHA Virtual Meeting

24 June 2020

BETTER POLICIES FOR BETTER LIVES

EAGMST Omics Reporting Frameworks

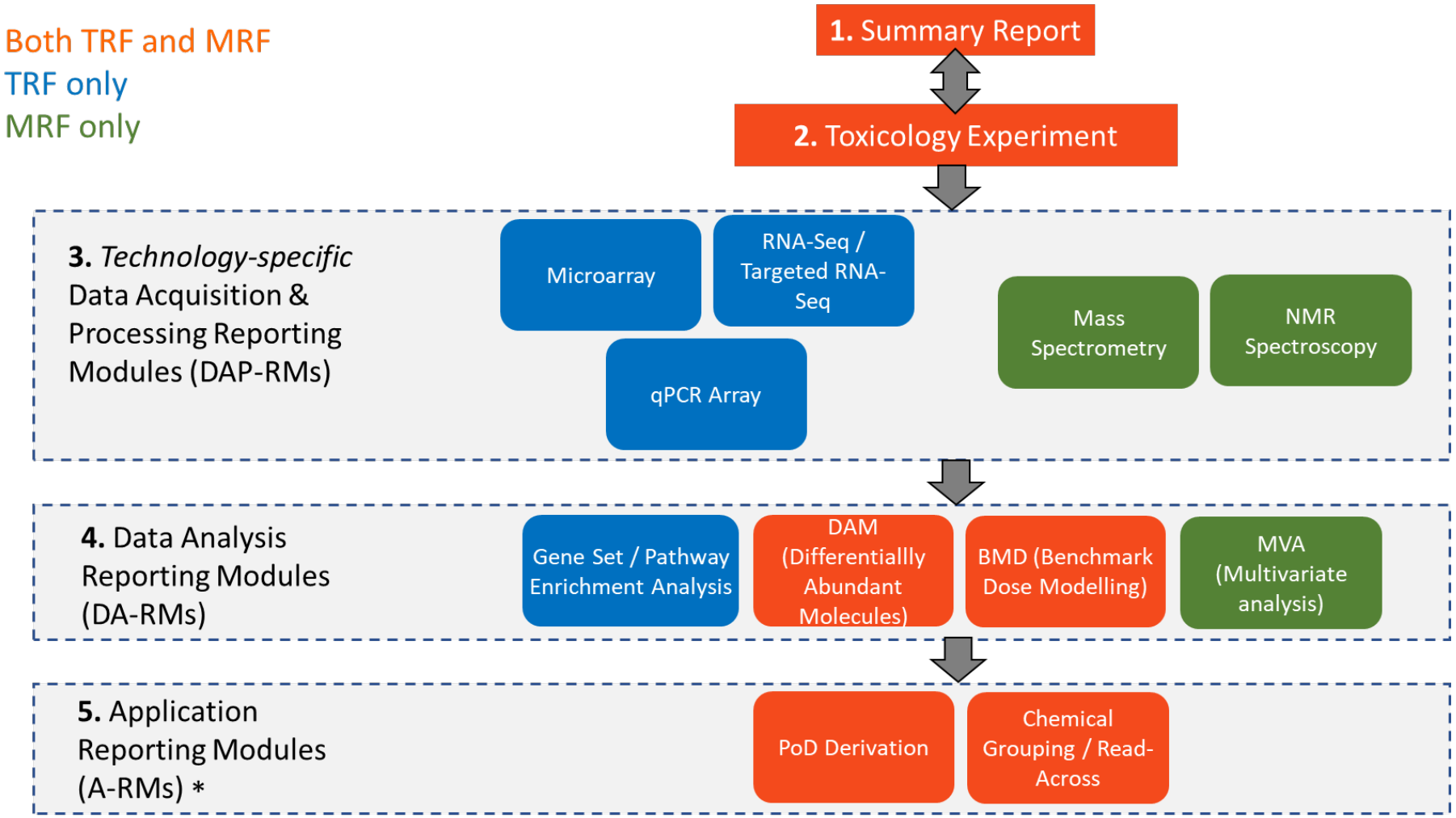
To develop frameworks for the standardisation of reporting of 'omics data generation and analysis, to ensure that all of the information required to understand, interpret and reproduce an 'omics experiment and its results are available.

Purpose: to ensure that sufficient information is available to enable an evaluation of the quality of the experimental data and interpretation, and support reproducibility.

NOT to stipulate the methods of data analysis or interpretation….**Rather**, provide guidance on reporting of information that fosters transparency and reproducibility.

Project Name	Project Leads
Metabolomics Reporting Framework (MRF)	Mark Viant (U. Birmingham, UK)
Transcriptomics Reporting Framework (TRF)	Joshua Harrill (USEPA) Carole Yauk (Health Canada)
Optimal Data Analysis Framework (ODAF)	Tim Gant (PHE, UK)/Florian Caiment (ECETOC C4 project)

Modular Structure of Omics Reporting Frameworks Harmonization of TRF and MRF



TRF Document, Major Topic Areas

TOXICOLOGY EXPERIMENT MODULE:

- Experiment should be described in sufficient detail to allow another researcher to replicate it.
- Adapted from existing sources
- Information in this section is independent of ‘omics platform

PROCESSING AND ANALYSIS OF ‘OMICS DATA MODULES:

- The transcriptomics technology, sample processing procedures, methods used to collect raw data and methods used to generate processed data.
- Described in Gant et al. (2017).
- Information in this section is dependent on ‘omics platform

DOWNSTREAM ANALYSIS REPORTING MODULES [DA-RMs]

- Detail the steps and resources necessary to reproduce a computational analysis of the processed data.

APPLICATION REPORTING MODULES [A-RMs]

- Details the steps used to further analyze the omics data and metadata specifically in the context of an application of regulatory interest.

TRF

Transcriptomics Reporting Framework (TRF)

Table of Contents

- **Stylistic alignment:**
  - Previous OECD guidance in the biological sciences (where applicable)
  - MERIT Project / Metabolomics Reporting Framework (MRF) – *In Progress*
- **Reporting Format**
  - Narrative text followed by Reporting Fields
  - Excel spreadsheet for reporting
- **Consistent vocabulary across modules**

Reporting structure

	A	B	C	D
1	**RELEVANT MODULE**	**REPORTING CATEGORY**	**REPORTING ELEMENT**	**DESCRIPTION OF ELEMENT**
2				
3	**Summary Report**	**Study identifier**	Unique study identifier	Unique code
4				
5		**Study rationale**	Objective of study	Controlled vocabulary: point-of-departure; hazard
6			Background information (supporting the objective)	Free text elaboration of above
7				
8		**Links to related study records**	Standardised toxicology dataset (e.g., linked to OECD	e.g. IUCLID ESR
9			Omics complete dataset (e.g., linked to MetaboLights,	e.g. MTBLSxx
10				
11	**Toxicology Experiment Module**	**Test item (chemical) and vehicle**	Test item name	
12			Test item identifier	SMILES or InChIKey
13			Vehicle name	
14				
15		**Test system characteristics**		
16		*EITHER in vivo*	a. Species	
17			b. Strain	
18			c. Sex	
19			d. Age	
20		*OR in vitro*	a. Cell type	
21			b. Species of origin	
22				
23		**Exposure conditions**	Test item concentration(s)	
24			Route of administration	
25			Schedule (single dose or repeated dosing)	
26			Frequency of repeated dosing	
27			Exposure duration(s)	
28				
29		**Biological samples**	Type (e.g., in vitro: cells, media, etc.; in vivo: cells, tissue, biofluid, whole organism, etc.)	
30			Sample preservation method (e.g., fresh, frozen, paraffin-embedded, etc.)	
31			Number of biological replicates per treatment	
32				
33	**TRF platform-specific data acquistion and processing Reporting Module**	**Sample preparation**	Sample preparation method (e.g., RNA extraction method, cell lysis, etc.)	
34				
35		**Technology**	Type (e.g., data acquisition and processing module used - DNA microarray, RNA-seq, etc.)	
36			Manufacturer(s) and model(s) (e.g., Agilent microarray, etc.)	

Study Summary revised | Experiment | Processing microarray data | DARM DEG

- **Executive summary included**
- **Modular**
  - **Flexible/expandable**
  - Add new modules as new platforms or analytical approaches released
- **Mandatory/optional reporting fields**
- **Database compatibility**
- **Summary, Experiment and DAM DARM harmonized with MRF**

TRF Case Study

Objective: review efficacy of TRF reporting modules through case studies

Submitter:
Andrew Williams
(Health Canada)

1) Identify dataset
2) Compute DEGs
3) Fill in TRF
   a) Microarray
   b) DAM DA-RM
4) Ease-of-use commentary

Referee:

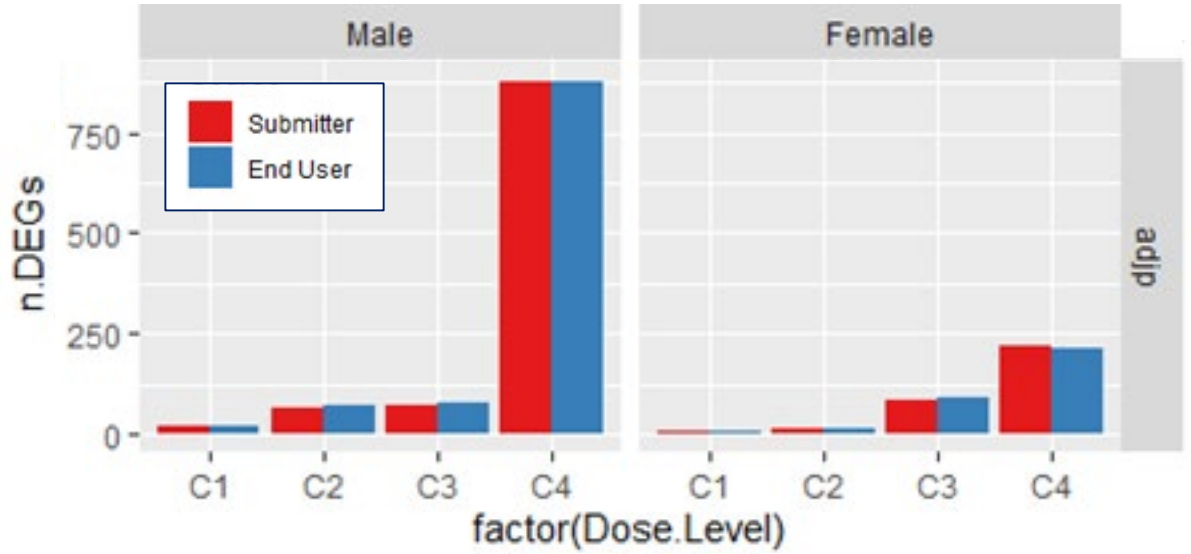
1) Provide completed TRF sans results to End User.

End User:
Leah Wehmas
(US EPA)

1) Review completed TRF
2) Reproduce DEG analysis
3) Ease-of-use commentary

Referee:

1) Concordance analysis
2) Summarize ease-of-use commentaries



Comparison of DEGs identified by Submitter and End User (adjp)

Case study next steps

Additional case studies:

- More developer and user feedback and participation
- Testing on different platforms (Affymetrix, RNA-seq)
- Testing different analytical platforms (open source in computing environment versus web application)
    - Application of RNA-seq data in the Optimal Data Analysis Framework case study

Section Workgroups

Title	Identity	Roles
Section Leads	Experiment — Raffaella Corvi [JRC] Microarray — Vikrant Vijay [NCTR] RNA-Seq — Florian Caiment [Maastricht] qPCR array — Jason O'Brien [ECCC] DARM.1 [DAM] — Lyle Burgoon [ERDC] DARM.2 [BMD] — Scott Auerbach [NIEHS] and Mark Viant [Birmingham]	Coordinate workgroup activities Maintain draft of section Manage timelines for deliverables
Workgroup Members	Variable	Contribute text and content for sections
"Floating" Facilitators	Joshua Harrill [US EPA] Carole Yauk [Health Canada]	Ensure consistency and cross-talk with other workgroups. Monitor progress in accordance with project timeline Foster discussion.
OECD Secretariat	Magda Sachana	Project administration / OECD liaison

All members of the TRF workgroup have the opportunity to comment on each section.

Project group leads (Harrill & Yauk) integrate sections into the final documents.

Project Timeline and Milestones **Completed**

Date	Milestones
April, 2018	Kickoff teleconference / recruiting for workgroups
June, 2018	Work initiated (P), Experiment (P), Microarray (P) and DARM.1 (P) modules
June, 2018	OECD WPHA & EAGMST Meeting – Project update (presentation), feedback incorporated
Dec, 2018	First drafts of Introduction (P), Experiment (P), Microarray (P) and DARM.1 (P)
March, 2019	Circulation of TRF (microarray) first draft to working group members for feedback/revision
June, 2019	Feedback from EAGMST (Summary module developed)
Dec, 2019	First complete TRF Introduction (P), Experiment (P), Microarray (P) and DARM.1 (P) Excel spreadsheet for data entry (P)
Dec, 2019	**Launch reproducibility case study to test microarray processing and DARM.1**
March 2020	First TRF application (Agilent microarray data set) complete at Health Canada – sent to EPA to test reproducibility (part 1 round-robin)
March 2020	First draft of RNA-seq data processing module completed (sent to team for review)
June 2020	First draft of the qPCR module complete
June, 2020	Harmonization of Summary, Toxicology Experiment, and DAM DARM with MRF

Upcoming Key Project Milestones

Date	Milestone
June 2020	Evaluate TRF reproducibility case study; revise; repeat for Affymetrix arrays
July, 2020	Working group revisions of qPCR processing module
Sept, 2020	**Launch of RNA-seq module reproducibility case study**
Sept, 2020	First draft of BMD modeling DARM.2
Dec, 2020	Launch qPCR and BMD [DARM.2] reproducibility case study
Dec, 2020	Reproducibility case study to test microarray processing and DARM.1 module complete
Dec, 2020	Complete RNA-seq and BMD [DARM.2] reproducibility case study
Jan, 2021	Complete TRF1 (microarray and DEG) case study; TRF ready for EAGMST review
March, 2021	Complete TRF2 (RNA-seq and DEG) case study; molecules ready for EAGMST review
May, 2021	Launch qPCR and BMD [DARM.2] reproducibility case study

MRF

MRF Expert Group

Title	Identity	Roles
Expert group members	Tripartite Industry Government / Regulator Academic ca. 15 very active members, ca. 10 ‘observers’	-Contribute expert knowledge and text wherever possible across the whole MRF guidance document -Ensure consistency of whole document
Facilitator	Mark Viant [Univ Birmingham]	-Foster discussion -Monitor progress in accordance with project timeline -Ensure consistency with TRF
Administrator	David Epps [Univ Birmingham]	-Meeting organisation
OECD Secretariat	Magda Sachana	-Project administration / OECD liaison

MRF builds on the Ecetoc MERIT project

MEtabolomics standaRds Initiative in Toxicology

nature COMMUNICATIONS

PERSPECTIVE

https://doi.org/10.1038/s41467-019-10900-y OPEN

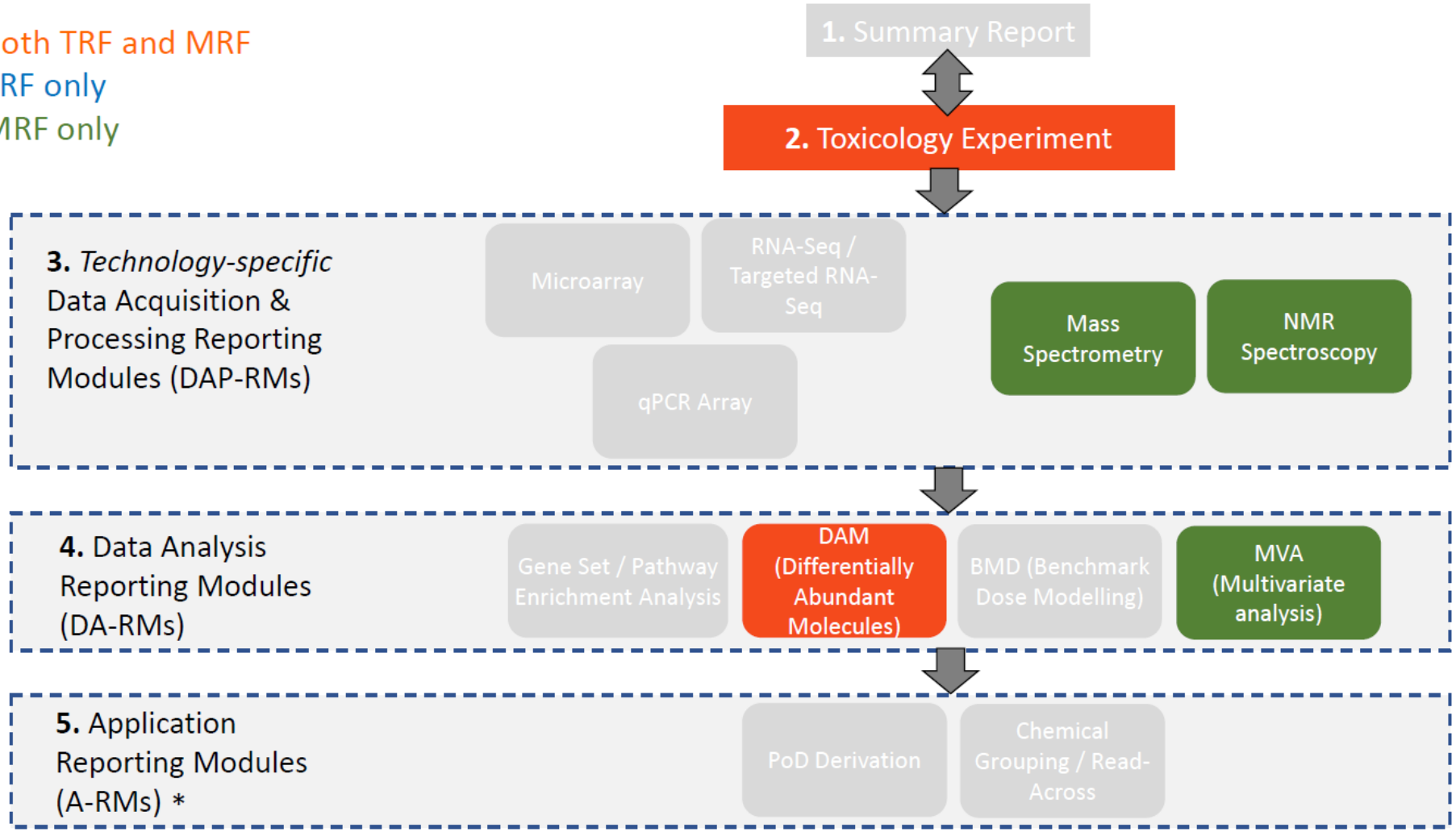
Use cases, best practice and reporting standards for metabolomics in regulatory toxicology

Mark R. Viant[1,12], Timothy M.D. Ebbels[2,12], Richard D. Beger[3], Drew R. Ekman[4], David J.T. Epps[1], Hennicke Kamp[5], Pim E.G. Leonards[6], George D. Loizou[7], James I. MacRae[8], Bennard van Ravenzwaay[5], Philippe Rocca-Serra[9], Reza M. Salek[10], Tilmann Walk[11] & Ralf J.M. Weber[1]

Published July 2019

Modular Structure of Omics Reporting Frameworks

Both TRF and MRF
TRF only
MRF only



5 modules finished

Modular Structure of Omics Reporting Frameworks

Both TRF and MRF
TRF only
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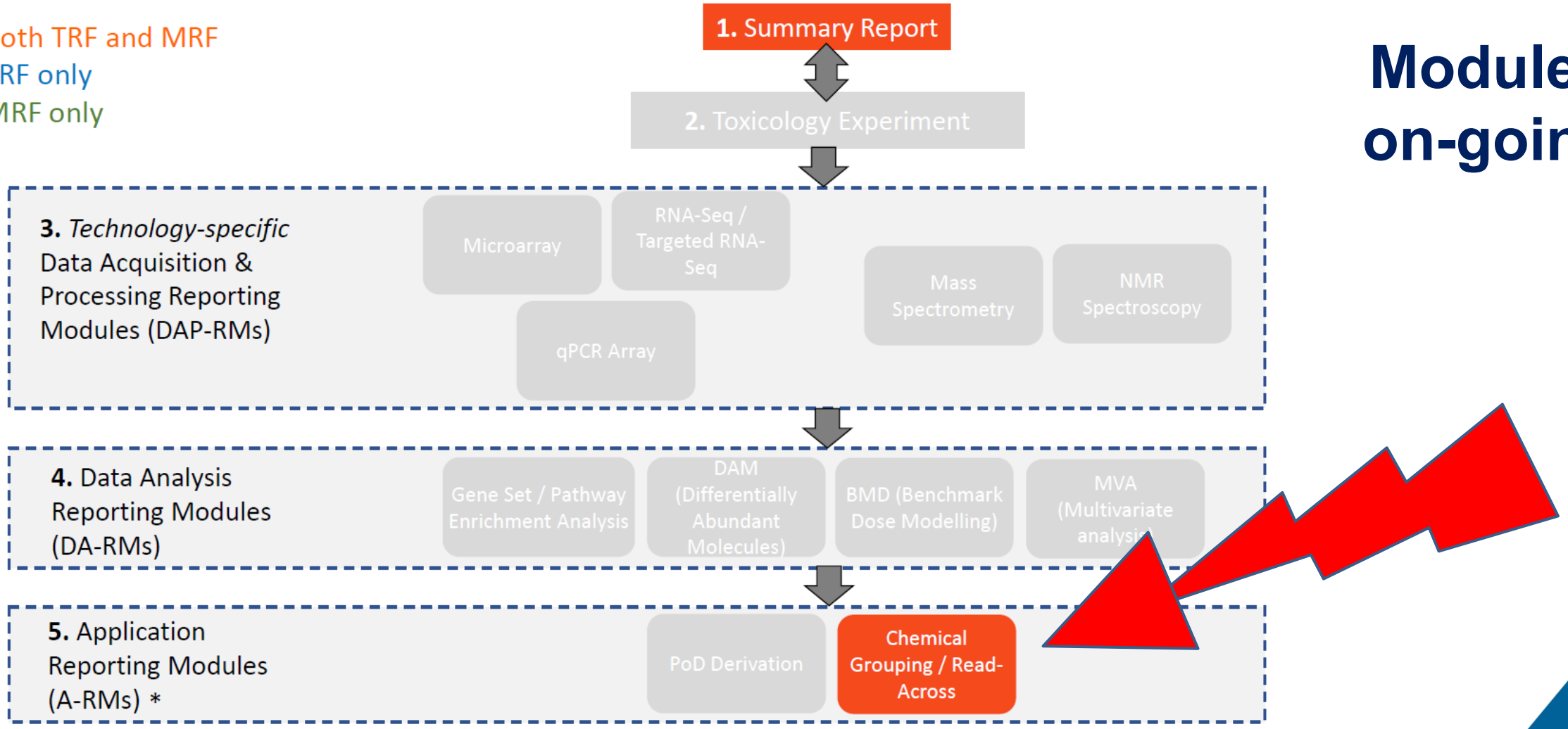

Modules on-going

First MRF

Table of Contents

- **Reporting Format**
  - Narrative text followed by Reporting Fields
  - Excel spreadsheet for reporting
- **Consistent vocabulary across modules**
- **Database compatibility**
- **ca. 80 page document**

Case Studies

Objective: review efficacy of MRF reporting modules through case studies

Steps

a) Identify investigators with completed ‘toxico-metabolomics’ datasets
b) Request these investigators complete and return the populated MRF reporting modules
c) MRF expert group review all feedback and update the MRF reporting modules

Progress to date

- Mass Spectrometry Module – currently under review by David Crizer, NIEHS (NTP)

We request more user testing and feedback!

MRF Project Timeline and Milestones Completed

Date	Milestones
Dec, 2018	Start of MRF project, kickoff teleconference
Feb, 2019	Expand MRF Expert Group to cover all topics
Feb, 2019	Review MERIT document (metabolomics reporting) for completeness
March, 2019	Work initiated on Mass Spectrometry, NMR Spectroscopy, Univariate statistical analysis and Multivariate statistical analysis modules
June, 2019	OECD WPHA & EAGMST meetings – Project update (presentation), feedback incorporated
Sept, 2019	First drafts of Univariate statistical analysis and Multivariate statistical analysis modules
March, 2020	First drafts of Mass Spectrometry, NMR Spectroscopy modules
March, 2020	Work initiated on Grouping / Read-Across module
May, 2020	First complete draft of Mass Spectrometry, NMR Spectroscopy, Differentially Abundant Molecules and Multivariate statistical analysis modules
June, 2020	Checked harmonisation of several modules with TRF
June, 2020	Begin first trial of Mass Spectrometry module
June, 2020	Draft MRF sent to OECD EAGMST for comment

MRF Upcoming Milestones

Date	Milestone
June, 2020	Receive feedback from OECD WPHA & EAGMST meetings, and integrate into MRF
July, 2020	Complete first draft of Grouping / Read-Across module
July, 2020	Begin first trials of NMR Spectroscopy, Differentially Abundant Molecules and Multivariate statistical analysis modules
Sept, 2020	Begin first trial of Grouping / Read-Across module
Sept, 2020	First draft of BMD modeling DARM.2 with TRF
Oct, 2020	Incorporate feedback from MS, NMR and DARM case study trials
Nov, 2020	Submit MRF Guidance Document to EAGMST for formal review (excluding BMD DARM and Application Reporting Modules)
Dec, 2020	EAGMST review

Further information

- Please contact: Magda Sachana

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