EMA/HMA European Platform for Regulatory Science Research

29th September 2025

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Overview

- Key results from 3 doctoral research projects
  - Study 1: Cross sectional analysis of CSR information via EMA 0070
  - Study 2: Systematic review and meta-analysis using CSR data obtained via EMA 0043
  - Study 3: Meta-analysis of safety data using CSRs obtained via EMA 0070 and 0043
- Implications & recommendation for regulatory perspective
- Implications for researchers

Study 1

Clinical Study Reports published by the European Medicines Agency 2016-2018: A cross-sectional analysis

Methods

Study Design:

- Cross sectional analysis of all CSRs from EMA 2016-2018 (policy 0070)
- For each CSR, obtained matched journal publication & trial registry

Analysis

1. Descriptive statistics of all available CSR information, summarised at the medication, trial and document levels
2. Descriptive statistics of subsection of 'pivotal' trials in each submission
3. Publication availability and timeliness

Methods

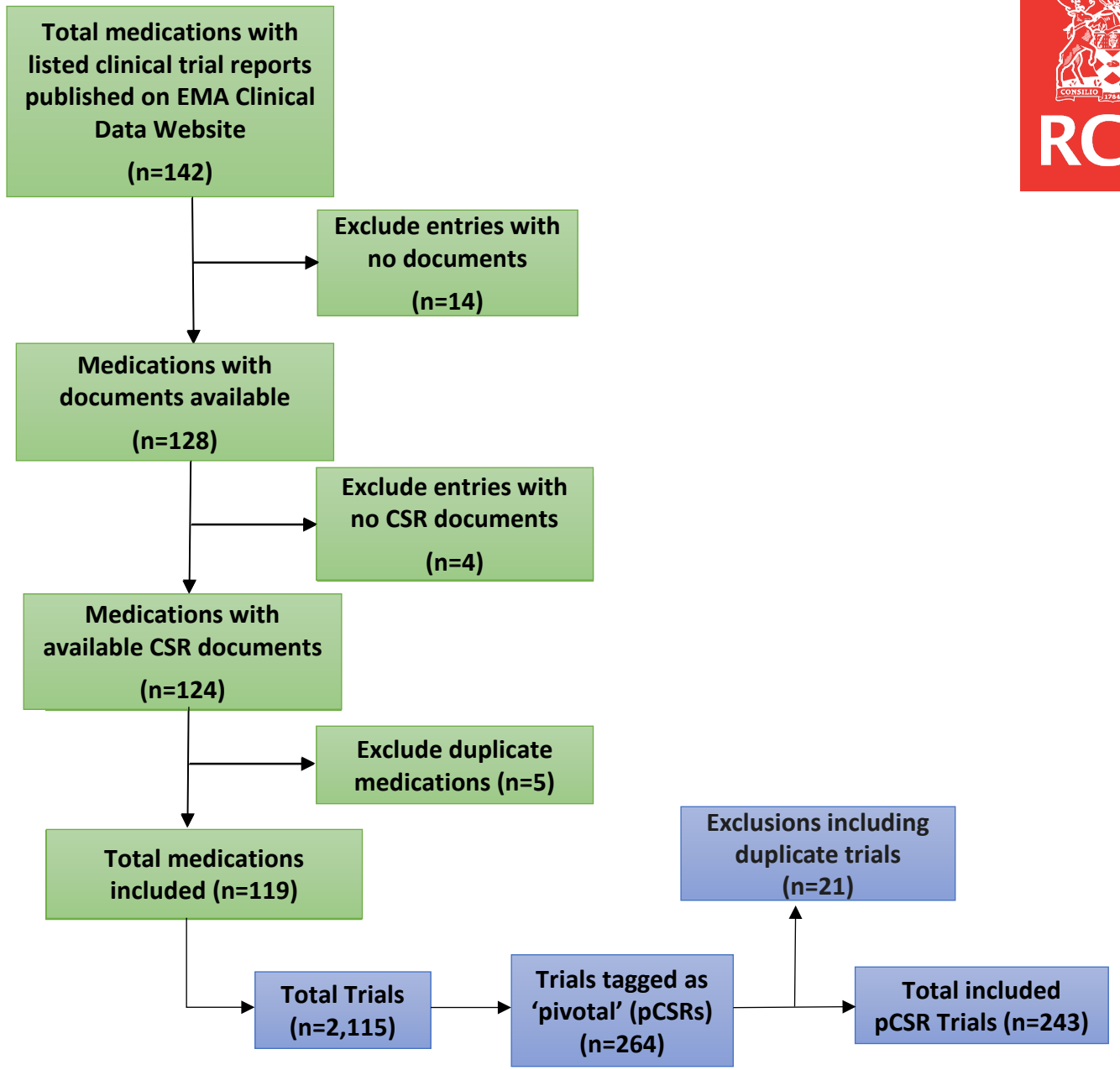
- Downloaded CSR files from EMA Clinical Data

- Filename (“m5351-(*trialid*)-p-csr-body”)
  - Individual trials
  - Pivotal (p-csr) or supportive (s-csr) trials
  - Type of documents (CSR body, protocol, sap, crf)

- Automatically extracted document length (R software)

Results

- 142 total medications
  - 119 after duplications
- 2,115 trials
  - 243 pivotal trials
- 6,301 documents



Key Results: All trials

Characteristics of CSRs

- Median per approval submission to the EMA
  - 15 (IQR 5-46) documents
  - 5 (IQR 2-14) trials
  - 9,629 (IQR 2,711-26,673) pages

- 55/119 (46.2%) submissions were supported by a single pivotal trial

- Of these 16/55 (29.6%) based on a single pivotal phase 1 trial

Key Results: Availability

Pivotal Trials

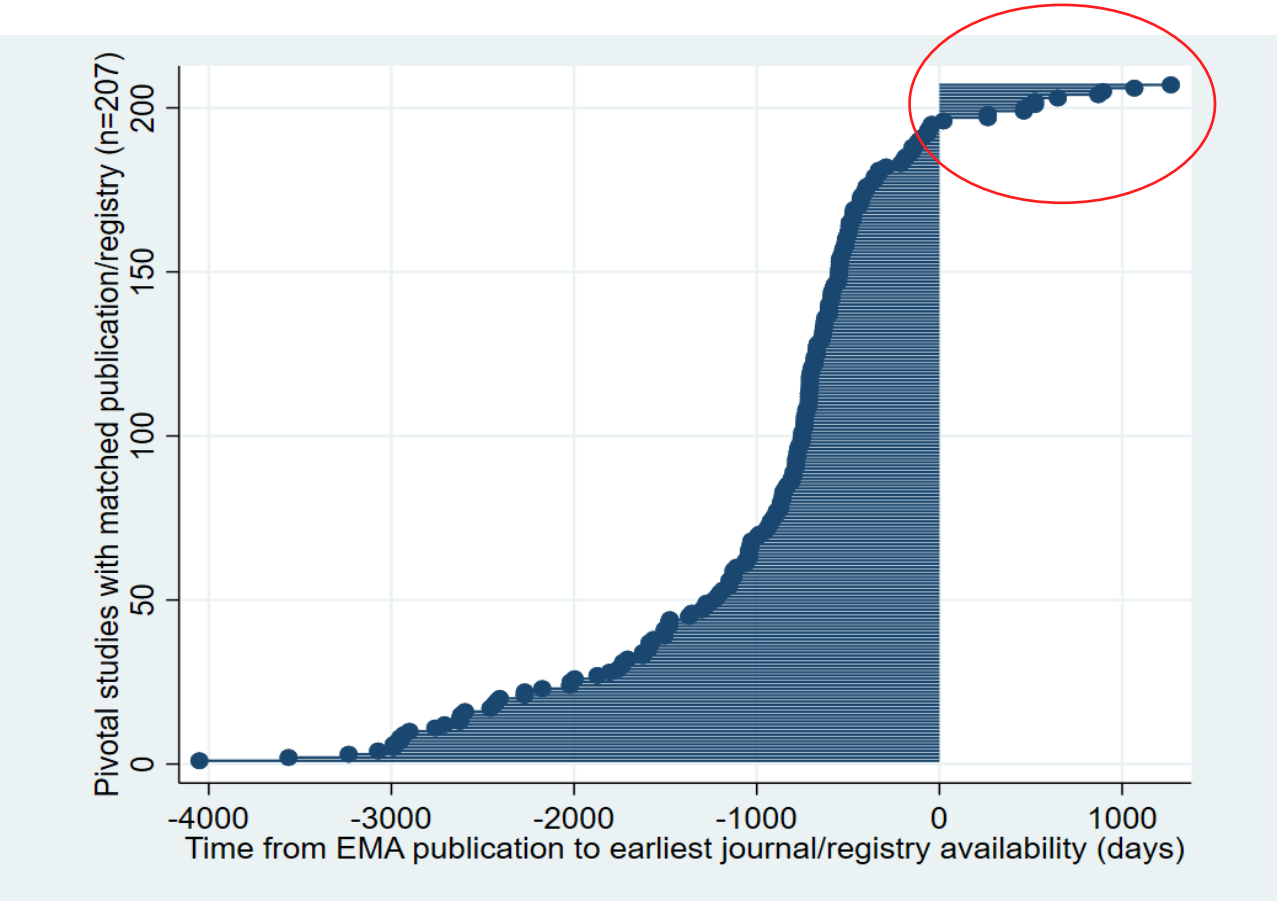
- No trial registry results (ClinicalTrials.gov) for 64/243 trials (26.3%)
- Journal publications were not located for 41/243 trials (16.9%)
- Neither clinical trial registry results, nor journal publications available for 33/243 trials (13.6%)

Key results: Timeliness

- Data from journal publication/registry were available prior to EMA in 94.5% (189/207)

- EMA publication was the **earliest source** in 5.5% (11/207)
  - Median 523 days (range 18-1,320) time difference between earliest source & EMA publication

Time to journal/registry publication relative to EMA publication for pivotal trials



Study 2

Efficacy and safety of sacubitril/valsartan in the treatment of heart failure: A systematic review incorporating unpublished clinical study

▸ HRB Open Res. 2021 Apr 1;3:5. Originally published 2020 Feb 10. [Version 2] doi: 10.12688/hrbopenres.12951.2

▸ Other versions

Efficacy and safety of sacubitril/valsartan in the treatment of heart failure: protocol for a systematic review incorporating unpublished clinical study reports

David Byrne [1,a], Tom Fahey [1], Frank Moriarty [1]

Methods: Systematic Review

- Sources:
  - Journal publications
  - Clinical trial registries
  - **Additional: CSRs requested from the European Medicines Agency (EMA) 0043**
- Data extracted separately from all 3 sources - Journal publications, Trial registries & CSRs
- Synthesis methods
  - Analysis 1: Meta-analysis using all 3 sources
  - Analysis 2: Sensitivity analysis – just publicly available sources (impact of CSR estimates)

Key results: Impact of using data from CSRs

- Data on effect estimates were only available from the CSR and were not available in published journal articles or from clinical trial registries
  - Highlights the importance of additional information which can be obtained from CSRs

- Use of CSRs
  - Reduction in magnitude - using just published information would have over-estimated QoL effect

Estimate using additional trial data from CSRs

RR 1.13 (95% CI 0.80-1.60)

Estimate using published sources only

RR 1.51 (95% CI 0.89-2.59)

- Reduction in magnitude - using just published information would have over-estimated QoL effect

CSRs: Practicalities

Availability

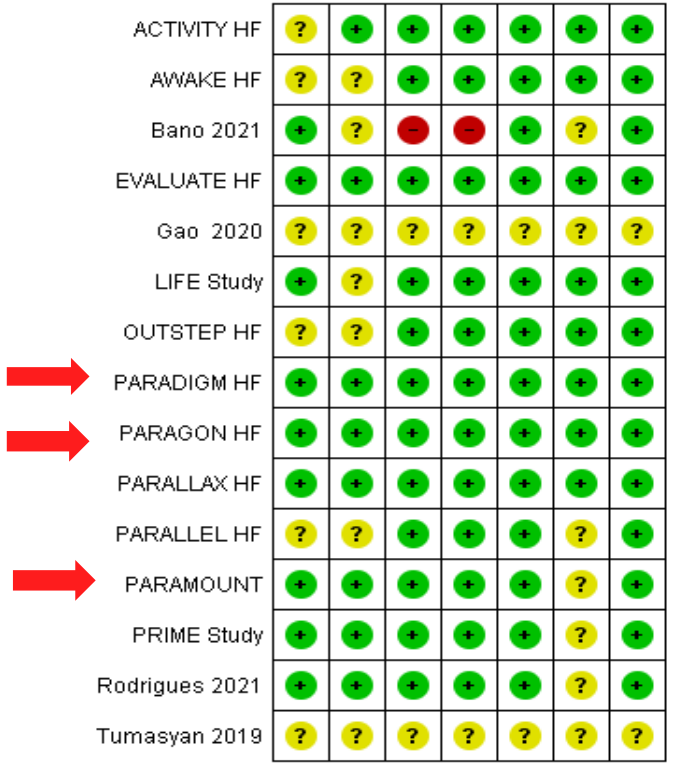
- CSRs available for 3 out of 15 trials
- Most trials completed after regulatory approval (2015)

Timeliness

- PARADIGM-HF CSR (Total 19,070 pages)
- EMA sent 353 pages (CSR body) via request under policy 0043
- Time for full CSR would be approx. 25 months

Trial data

- Limited additional data for MA vs. published sources
- Aggregate data



Study 3

Reporting of adverse events in clinical study reports of SGLT2 inhibitors submitted to the European Medicines Agency compared with trial registries and publications: A cross sectional study

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Methods

1. Completeness and consistency of adverse outcome reporting across CSRs (obtained via 0043 and 0070), publications & trial registry
    - Cross sectional analysis

2. Impact of safety data from CSRs on estimates of effect
    - Meta-analysis using data from all 3 sources

CSRs

Publications

Trial registries

ClinicalTrials.gov

Key Results: Completeness of AE reporting

- CSRs from 39 trials

Outcome	CSR (n=39)	Registry (n=43)	Publication (n=44)
OAE	100% (39/39)	100% (43/43)	95.5% (42/44)
SAE	100% (39/39)	100% (43/43)	100% (44/44)
Mortality	100% (39/39)	2.3% (1/43)	93.2% (41/44)
Ketoacidosis	28.2% (11/39)	20.9% (9/43)	4.6% (2/44)
Urinary Tract Infection	100% (39/39)	27.9% (12/43)	77.3% (34/44)
Genital Infection	97.4% (38/39)	0% (0/43)	45.5% (20/44)
Volume Depletion	79.5% (31/39)	9.3% (4/43)	36.4% (16/44)
Acute Kidney Injury	66.67% (26/39)	6.9% (3/43)	36.4% (16/44)
Amputation	23.1% (9/39)	2.3% (1/43)	2.3% (1/44)
Necrotising Fasciitis	12.8% (5/39)	2.3% (1/43)	0% (0/44)
Fracture	79.5% (31/39)	74.4% (32/43)	18.2% (8/44)

OAE=Overall Adverse Events SAE=Serious Adverse Events

Key Results: Inconsistency of reporting

- Inconsistency in almost a quarter (24.4%) of cases, with a greater number of events reported in publications compared with CSRs.

- For 65.2% (260/399) there were a greater number of events reported in the CSR compared with trial registry

Key Results: Meta-analysis

- Change in magnitude of effect and levels of significance for outcomes (OAE, SAE, mortality and genital infection) using CSRs compared with published sources

- Overall, meta-analysis showed an increased risk for two outcomes:
  - Amputations (RR 1.24; 95% CI 0.84-1.85)
  - Necrotising fasciitis (RR 1.73; 95% CI 0.27-10.98)

Implications & Recommendations

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Summary of work

1. **Landscape of currently available CSRs via 0043**
   - In depth overview of CSRs available from EMA via policy 0070
   - Outlined novel techniques of navigating CSRs
   - Highlighted benefits and challenges of requesting and dealing with CSRs practically

2. **Impact of CSRs in evidence synthesis**
   - Application of CSR-informed evidence to novel medications for chronic diseases
   - CSRs provide access to more complete results
   - Showed impact on efficacy, safety, QoL outcomes
   - Limitations of CSRs in cases of drug approvals based on pivotal trials

3. **Timeliness**
   - CSRs can be a more timely source
   - Variation in the timeliness and completeness of CSRs across sources
   - Access to full CSRs can be a barrier to use

Implications

Research	Policy	Clinical
• Benefits in use of CSRs in evidence synthesis • Research methodology – navigating CSRs under 0070	• Highlighted issues with timeliness of access to CSRs • Updating criteria on use of CSRs in SR and MA	• Safety outcome reporting • Post-trial outcome reporting
<u>Relevant to:</u> • Systematic reviewers • Health Technology Assessors	<u>Relevant to:</u> • Drug regulators (EMA/FDA) • Pharmaceutical industry • Healthcare decision makers	<u>Relevant to:</u> • Drug regulators (EMA/FDA) • Healthcare Professionals • Patients

Conclusions

- CSRs provide the most complete and timely source of evidence for many trials, and occasionally the only source
- Access to CSRs via proactive policy 0070 is most effective
- Use of evidence from CSRs can confer a change in results for evidence synthesis including efficacy, safety and adverse outcomes
- Lack of availability of CSRs may be a barrier for researchers and other end-users to efficiently and effectively use such data in research

Implications and recommendations

- Researchers should be aware of the current practical aspects of requesting and using CSRs in evidence synthesis, including differences in evidence using EMA policy 0043 and 0070

- Regulators/the EMA should continue the proactive release of full CSRs via the restarted 0070 process

- Ultimately, all data pertaining to clinical trials should be made publicly available following completion of the study

Acknowledgements

Funding: This research was funded by the Health Research Board of Ireland as part of the RightCare Collaborative Doctoral Award (CDA-2018-005).

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Thank you