**RAPIDO**

A ‘Flash-Mob’ UK national audit of the use of **R**eversal **A**gents in **P**atients ant**I**coagulated with **D**irect **O**ral anticoagulants (HaemSTAR RAPIDO)

**Guide for local NHS audit department registration**

Website: <https://haemstar.org/RAPIDO/>

Contact: richard.buka@nhs.net

**Contents**

[Welcome 3](#_Toc97120366)

[Local audit registration 4](#_Toc97120367)

[Quick-start guide 4](#_Toc97120368)

[Project summary 7](#_Toc97120369)

[One-line summary 7](#_Toc97120370)

[Project oversight 8](#_Toc97120371)

[Audit standards 9](#_Toc97120372)

[Frequently asked questions 11](#_Toc97120373)

[Appendix 1: Data to be collected 13](#_Toc97120374)

# **Welcome**

Please use this document to guide your local audit department registration. As every organisation is different, this is not a simple ‘plug in and play’ guide but it should include all the information you require. If you need any further information or have any questions, please email project lead, Richard Buka – richard.buka@nhs.net.

We have also tried to pre-empt any questions that your audit department may raise. These questions and their answers can be found in this document.

|  |
| --- |
| **Local audit registration****Quick-start guide** |
| Audit title | A ‘Flash-Mob’ UK national audit of the use of **R**eversal **A**gents in **P**atients ant**I**coagulated with **D**irect **O**ral anticoagulants (HaemSTAR RAPIDO) |
| Main speciality | Clinical Haematology |
| Supervisor | *Please insert name of local haematology consultant* |
| Aims | To audit the use of reversal agents for patients taking direct oral anticoagulants who present with bleeding |
| Objectives | **Primary:** * To audit the use of reversal agents for anticoagulation against clinical guidelines1–3 and national body recommendations (see page 3).4,5

**The primary audit standards assessed will be** * Proportion of patients treated with a reversal agent who had severe or life-threatening bleeding as defined by the International Society for Thrombosis and Haemostasis6
* Proportion of patients treated with a reversal agent who received treatment in accordance with the dosing schedule laid out in the relevant summary of product characteristics (SPC)

**Secondary objectives / outcomes*** Exploratory data collection around comparative efficacy of reversal agents to inform design of future randomised clinical trials.
* Specifically, we will collect data on:
	+ Thrombotic events within 90 days
	+ Requirement for transfusion within 90 days
	+ Death within 90 days
	+ Death due to bleeding within 90 days
	+ Death due to thrombosis within 90 days
 |
| Scope | National – UK-wide audit of use of high-cost medicines |
| Type of project | National guideline |
| Please give the name of the local/national guidelineYour audit department may ask for specifics of the audit standards which are listed here. | **Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. Technology appraisal guidance (TA697). 12 May 2021.**[www.nice.org.uk/guidance/ta697](http://www.nice.org.uk/guidance/ta697) * Page 4, paragraph 1.1 and 1.2
	+ 1.1: "Andexanet alfa is recommended as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if:
		- the bleed is in the gastrointestinal tract, and
		- the company provides andexanet alfa according to the commercial arrangement."
	+ 1.2: "Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing randomised trial mandated by the regulator."

**Makris et al on behalf of the British Committee for Standards in Haematology (BCSH). Guideline on the management of bleeding in patients on antithrombotic drugs. British Journal of Haematology, 2012,160,35–46 doi:10.1111/bjh.12107guideline** (<https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12107>) * Page 40
	+ Direct oral Xa inhibitors - Rivaroxaban and Apixaban
	+ Paragraph 5: *"Recommendations"*
		- “There is no specific antidote for rivaroxaban. Management of bleeding should be through cessation of treatment and general haemostatic measures"
		- "In situations with ongoing life-threatening bleeding, PCC, APCC and rFVIIa should be considered”

**Addendum to above guideline (2018). Alikhan R**. (<https://b-s-h.org.uk/media/16887/addendum-2018-dabigatran-idarucizumab-raz.pdf>)* Page 2:
* *Paragraph 1: Recommendation*
* Idarucizumab (Praxbind) is a specific reversal agent for dabigatran (Pradaxa) and is indicated for adult patients treated with dabigatran when rapid reversal of its anticoagulant effect is required
	+ Life-threatening or uncontrolled bleeding
	+ Emergency surgery or urgent invasive procedure
	+ The dose of idarucizumab is 5g (2 x 2.5g/50ml) administered intravenously as a bolus injection
 |
| Reason for audit | To assess compliance with national guidelines. |
| Methodology | Retrospective |
| Sample population | **Inclusion criteria*** Individuals ≥18 years of age
* Taking apixaban, dabigatran, edoxaban or rivaroxaban in any dose and frequency, for any indication
* Treated with andexanet alfa, idarucizumab, or prothrombin complex concentrate (PCC) to mitigate bleeding or the risk of bleeding
	+ For bleeding of any severity
	+ Prior to surgery of any urgency or bleeding risk
* Treated from 1st October 2020
 |
| Sample size | Likely 25-200 per NHS organisation |
| Sample selection method | All patients who meet inclusion criteria |
| Data collection method | Case note review |
| Audit/data collection tool | See attached full protocol |
| Estimated start date | 1st May 2022 |
| Estimated end date | 31st November 2023 |
| Data collection windows | Data to be collected in two windowsMay-July 2022To collect data from 1st October 2020 to 31st January 2022October-December 2023To collect data from 31st January 2022 to 30th June 2023 |
| Estimated presentation dates | 1st April 2023 (presentation of interim data)1st April 2024 (presentation of full data) |

**How to find patients who may be eligible for the audit?**

Although every site will require a slightly different approach, we recommend the following steps to identify patients.

1. Acquire a list of patient numbers from hospital pharmacy and/or blood bank depending on where each product (andexanet alfa, PCC (beriplex or octaplex), idarucizumab) is stocked.
2. Screen patients who have received PCC to exclude patients receiving this for indications other than DOAC-reversal (e.g. warfarin reversal or DIC).

# **Project summary**

The vast majority of patients taking direct oral anticoagulants (DOACs) in the UK take an anti-factor Xa medication which includes apixaban, rivaroxaban, and edoxaban. British Society of Haematology guidelines for the Management of Bleeding in Patients on Antithrombotic Agents1 recommend that:

* There is no specific antidote for rivaroxaban. Management of bleeding should be through cessation of treatment and general haemostatic measures.
* In situations with ongoing life-threatening bleeding, PCC … should be considered.

These guidelines were written prior to the widespread use of apixaban and edoxaban but the use of PCC is generally accepted for treatment of patients taking these drugs who present with bleeding.

A 2018 addendum recommended the use of idarucizumab for patients taking dabigatran who have major bleeding.2 In 2021, NICE approved the use of Andexanet alfa for treatment of patients taking apixaban and rivaroxaban who have acute, major gastrointestinal bleeding.4 However, andexanet alfa is approved for use in all patients with major bleeding in Scotland.5

Despite these recommendations, empirical data to support the use of reversal agents is lacking. The use of idarucizumab and andexanet alfa are supported by single-arm trials and real-world analyses.7,8 PCC use is supported by retrospective, observational studies only.

Importantly, these agents are high-cost drugs with the typical cost of PCC at nearly £3,000 per treatment and andexanet alfa at £15,000 - £23,000 per dose. There are therefore substantial cost implications to the NHS and real-world data is urgently required to appraise the use of these drugs in the UK. Secondary aims of this project are to report the outcomes of patients who are treated with these drugs and to compare their efficacy.

# **One-line summary**

This national project aimsto audit the use of reversal agents in patients treated with direct oral anticoagulants (DOACs) who are bleeding.

# **Project oversight**

 **Project lead**

Dr Richard Buka
Academic Clinical Fellow
Institute of Cardiovascular Sciences
University of Birmingham
Birmingham
UK

Honorary Haematology Registrar
University Hospitals Birmingham NHS Foundation Trust
Birmingham
UK

richard.buka@nhs.net

**Senior investigator**

Dr Pip Nicolson
Clinical Lecturer
Institute of Cardiovascular Sciences
University of Birmingham
Birmingham
UK

Honorary Haematology Registrar
University Hospitals Birmingham NHS Foundation Trust
Birmingham
UK

pnicolson@nhs.net

**Project Office**

Birmingham Centre for Observational and Prospective Studies
University of Birmingham
Birmingham
UK

bhamred@contacts.bham.ac.uk

**Project coordination**

HaemSTAR ([www.haemstar.org](http://www.haemstar.org))

**Ethical approval**

As this project is an audit, formal ethical approval is not required. This has been confirmed with the University of Birmingham BiCOPS team and the NIHR “Is my study research?” tool.

# **Audit standards**

**Reference guidelines and recommendations**

**ISTH 2010**6Schulman et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients.

* Contains definitions for major bleeding

**BSH 2012**1
Makris et al. Guideline on the management of bleeding in patients on antithrombotic agents.

* There is no specific antidote for rivaroxaban. Management of bleeding should be through cessation of treatment and general haemostatic measures.
* In situations with ongoing life-threatening bleeding, PCC … should be considered.

**BSH 2018**2

* Idarucizumab (Praxbind) is a specific reversal agent for dabigatran (Pradaxa) and is indicated for adult patients treated with dabigatran when rapid reversal of its anticoagulant effect is required for:
	+ Life-threatening or uncontrolled bleeding
	+ Emergency surgery or urgent invasive procedure
	+ The dose of idarucizumab is 5g (2 x 2.5g/50ml) administered intravenously as a bolus injection

**CHEST 2018**3
Lip et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report

* The vast majority of bleeds can be managed conservatively with temporary discontinuation of NOACs (DOACs) and supportive measures. Reversal agents should be used sparingly in the cases of severe and life-threatening bleeding, which includes bleeding causing hemodynamic compromise, ICH, bleeding into a critical organ or closed space, persistent bleeding despite general supportive measures and local hemostatic support, or risk of recurrent bleeding due to excess NOAC drug exposure due to delayed clearance of NOAC (eg, acute renal failure) or overdose.

**SMC 2020**5Scottish Medicines Consortium. Andexanet alfa (Ondexxya)

* **Andexanet alfa (Ondexxya®)** is accepted for use within NHS Scotland on an interim basis subject to ongoing evaluation and future reassessment.
	+ For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

**NICE 2021**9Technology Appraisal Guidance. Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban

* Andexanet alfa is recommended as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if the bleed is in the gastrointestinal tract
* Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing randomised trial mandated by the regulator.

# **Frequently asked questions**

**How many people can be involved in the project at one centre?**

At each centre, you can have a team of up to 10 people. Occasionally, large centres, or centres where there is rapid staff turnover may need more and in this situation, please email the BiCOPS team. In fact, we strongly encourage wide and inclusive participation. All we ask is that one person is nominated as the centre’s point of contact. Every individual who contributes one full record will be recognised with citable collaborator status (equivalent to authorship) in future presentation(s) and publication(s).

**Will patient data be anonymised?**

Yes, the data will be fully anonymised although we will collect basic demographics including age, sex, and ethnicity. We will not collect patient identifiers such as names, NHS numbers, local ID numbers, or dates of birth centrally. The data collection tool will assign a unique project number (REDCap record ID) to each patient that you enter. However, in order to answer any future data queries, a local list that links record IDs with local identifiers should be kept on a secure, password-protected NHS computer.

**Will the data that I enter be credited to my site?**

Yes. The data you enter will be linked to your institution. Most importantly, we will use this data to provide, on request, each centre with a summary of their own data.

We may also use this data to compare sites in general terms as defined by criteria such as their location within the UK e.g. Scotland *versus* England or academic *versus* non-academic centres. The data will however remain confidential, and names of individual sites connected to specific data will not be reported in any future presentations or publications.

**How is data collected, where will it be stored, and how will it leave my NHS organisation?**

Anonymised data will be entered directly onto REDCap which is a secure web application for building and managing online databases. Clinical teams at participating sites will ensure that participants’ anonymity is maintained when entering data into the REDCap system. REDCap has been used extensively to electronically capture and store sensitive health data in a secure and encrypted format for similar projects within the NHS. The University of Birmingham is already a partner with REDCap and HaemSTAR has used the system twice before for national audit projects. Data will be collected and stored in accordance with the General Data Protection Regulation (2016). Direct access to the audit data will be restricted to members of the management committee and audit team at the Birmingham Centre for Observational and Prospective Studies. Access to the database will be overseen by the data manager.

**Is ethical approval required and do patients need to give consent?**

This project is an audit and as such, ethical approval is not required. Data will not be used to make recommendations about future patient treatment. Data collection is retrospective and will not interfere directly with patient care. Similarly, patient consent is not required. This has been confirmed with the Birmingham Centre for Observational and Prospective Studies and confirmed using the NIHR online tool “Is my project research?”.

**How will the findings be disseminated?**

We plan to present interim data nationally and internationally at the British Society of Haematology Annual Scientific Meetings and American Society of Haematology Annual Meetings. Following completion of the project, findings will be submitted to a reputable peer-reviewed scientific journal for publication.

**How will contributors and my organisation be recognised?**

Fair recognition is a core HaemSTAR value and HaemSTAR has adopted a collaborative authorship model. This means that all contributors to this project will be recognised by name as citable collaborators (equivalent to co-authors) in future publications.

**What is HaemSTAR?**

HaemSTAR is UK-wide network organisation of clinical haematology trainees who are interested in research in non-malignant haematology. It is supported by the National Institute of Health Research and is a non-profit organisation. More information can be found at [www.haemstar.org](http://www.haemstar.org).

**Who are BiCOPS?**

The Birmingham Centre for Observational and Prospective Studies (BiCOPS), part of the University of Birmingham, facilitate the conduct of clinical audits and prospective observational cohort studies. They will be working with the HaemSTAR collaborative on RAPIDO providing methodological advice, the bespoke database, project management and data integrity and statistical analysis.**Appendix 1: Data to be collected**

**Demographic data and medical history**

* Hospital site
* Age
* Sex
* Ethnicity (Office of National Statistics categories)
* Weight
* Height

**Comorbidities**

* Active cancer
	+ Primary site
	+ Presence of cerebral metastases
* Atrial fibrillation
* Congestive cardiac failure
* Dementia
* Ischaemic heart disease
* Liver disease
* Peripheral vascular disease
* Prior major bleeding
* Prior thrombosis – arterial
* Prior thrombosis – venous
* Renal disease
* Surgery in last 6 months

**Relevant concurrent medications**

* Antihypertensives
* Antiplatelets
* Antidepressants

**Social history**

* Alcohol intake
* None
* ≤14 units / week
* >14 units / week
* Smoking history
* Current
* Non-smoker
* Ex-smoker

**Information about DOAC treatment**

* Which DOAC they are taking
* At what dose (mg)
* Hours since last taken if known

**Information about bleed**

* Date of bleed onset
* Time of bleed onset
* Bleeding site
	+ Gastrointestinal
	+ Intracranial
		- Site of haemorrhage: infratentorial or supratentorial
		- Intracranial bleed volume if known (ml)
		- Intraventricular haemorrhage Y/N
		- Worst GCS in first 6 hours from bleed onset (3-15)
	+ Other – please give details
* Spontaneous, or secondary to injury or other provoking factor
* Vital signs
	+ Lowest systolic blood pressure before administration of reversal agent
	+ Highest heart rate before administration of reversal agent

*Information will be used to categorise bleeding according to defined international criteria (ISTH). Information will also be used to retrospectively calculate Glasgow-Blatchford Bleeding Score and Rockall scores, for upper gastrointestinal haemorrhage or ICH score for intracranial haemorrhage where applicable.*

**Investigations at bleed onset**

* Haemoglobin
* Platelets
* Creatinine
* Urea
* DOAC level

**Prior investigations**

* Haemoglobin in last 12 months
* Creatinine level in last 12 months

**Reversal**

* Which reversal agent was used
* Dosing of reversal agent

**Tranexamic acid**

* Was tranexamic acid given?

**Transfusions**

* Were red cells transfused prior to administration of reversal agent?
	+ How many units?
* Were red cells transfused after administration of reversal agent?
	+ How many units?
* Was FFP transfused prior to administration of reversal agent?
	+ How many units?
* Was FFP transfused after administration of reversal agent?
	+ How many units?
* Were platelets transfused prior to administration of reversal agent?
	+ How many units?
* Were platelets transfused after administration of reversal agent?
	+ How many units?

Was there any loss of consciousness, collapse, or syncope at any time preceding or up to 4 hours following administration of the reversal agent?

**Surgery / procedures**

* Was surgery or a procedure planned or performed as part of the management of this bleeding episode?
	+ Was this performed?
	+ How many hours after administration of the reversal agent was this procedure performed?

**Follow-up blood tests**

* Hb at ~24h following administration of reversal agent
	+ Leave blank if no Hb performed between 24 and 48 hours post-administration of reversal agent

**Follow-up**

***Intracranial bleeding only***

* Was any further neuroimaging performed 6-24 hours after administration of the reversal agent?
	+ How many hours after?
	+ Status of haematoma (stable, expanding)
* What was GCS 6-24 hours after administration of the reversal agent?
* Was there any functional neurological deterioration at discharge or day +30 whichever is sooner?

**Resumption of anticoagulation**

* Was anticoagulation planned to restart in the 90 days following administration of the reversal agent?
	+ How many days was planned?
* Was anticoagulation restarted within 90 days or was there documentation of a plan to restart?
	+ If so, when?

**Incidence of thrombosis**

* Was the patient diagnosed with a thrombotic episode at any point in the following 90 days post-treatment with the reversal agent
* If so, details:
	+ Venous / arterial
	+ Site: PE / DVT / Other venous / Stroke / MI / Other arterial
* Did patient die in the follow-up period?
	+ If so, how many days post-reversal agent did death occur?

**Further bleeding episodes**

* Any further bleeding episodes requiring more treatment?
	+ To be inputted in the database as a separate episode

**References**

1. Makris M, Van Veen JJ, Tait CR, Mumford AD, Laffan M. Guideline on the management of bleeding in patients on antithrombotic agents. Br J Haematol. 2013;160(1):35–46.

2. Alikhan R. Addendum to guideline on the management of bleeding in patients on antithrombotic agents. Br J Haematol. 2018;

3. Lip GYH, Banerjee A, Boriani G, Chiang C en, Fargo R, Freedman B, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest [Internet]. 2018;154(5):1121–201. Available from: https://doi.org/10.1016/j.chest.2018.07.040

4. National Institute for Health and Clinical Excellence. Appraisal consultation document Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. (September 2020):1–18.

5. Scottish Medicines Consortium. Andexanet alfa (Ondexxya) [Internet]. 2020 [cited 2020 Oct 13]. Available from: https://www.scottishmedicines.org.uk/medicines-advice/andexanet-alfa-ondexxya-full-smc2273/

6. Schulman S, Anger SU, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010;8(1):202–4.

7. Coleman C, Dobesh P, Danese S, Ulloa J, Lovelace B. Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study. Future Cardiol [Internet]. 2020 Jul 3 [cited 2020 Oct 13]; Available from: https://www.futuremedicine.com/doi/abs/10.2217/fca-2020-0073

8. Brown CS, Scott RA, Sridharan M, Rabinstein AA. Real-world utilization of andexanet alfa. Am J Emerg Med [Internet]. 2020 Apr 1 [cited 2020 Oct 13];38(4):810–4. Available from: https://pubmed.ncbi.nlm.nih.gov/31870672/

9. National Institute for Health and Care Excellence. Technology Appraisal Guidance. Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. 2021.