A contemporary framework for understanding mortality in people with congenital hemophilia A (PwcHA)

Steven W. Pipe,1 Rebecca Kruse-Jarres,2 Johnny N. Mahlangu,3 Glenn F. Pierce,4 Flora Pevvandi.⁵ Fabian Sanabria.⁶ Peter Kuebler.7 Richard H. Ko.7 Tiffany Chang.7 Charles R.M. Hav8



Summary



The hemophilia treatment landscape is rapidly





We identified a need for a unified approach for reporting types and causes of death to better understand mortality in persons with congenital hemophilia A (PwcHA).



The framework presented here enables the consistent and objective assessment of fatalities



Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, MI, USA; ²University of Washington, Seattle, WA, USA and Washington Center for Bleeding Disorders, Bloodworks Northwest, Seattle, WA, USA; 3University of the Witwatersrand and NHLS, Johannesburg, South Africa; 4World Federation of Hemophilia, Montreal, Canada; 5IRCCS Ca' Granda Foundation, Ospedale Maggiore Policlinico, Milan, Italy; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Genentech, Inc., South San Francisco, CA, USA; SUK National Haemophilia Database,

Manchester, UK and Manchester Royal Infirmary, Manchester, UK



- Despite advances in therapies for hemophilia A (HA). PwcHA currently. have a shorter life expectancy compared with males in the general
- The treatment landscape of HA is evolving rapidly and substitution and gene therapies offer the prospect of improved efficacy and decreased treatment burden, 1-4
- However, compared with traditional clotting factor concentrates, the safety profiles of newer agents in the real world are limited, and may be different based on their mechanism of action.5
- In addition, safety reports which are published after new agents are approved may lack key contextualizing data, making it difficult to interpret the safety data.
- A consistent approach to reporting fatal events and causes of death is needed to better understand deaths in PwcHA. This will enable better assessments of the risks and benefits of treatments and allow the impact of the treatment on the hemophilia community to be monitored.
- Here we aim to provide a contemporary understanding of causes of death in PwcHA and a framework allowing for the consistent interpretation of fatal events and analyses of mortality trends of past, present, and future hemophilia therapeutics



Methods

Causes of mortality in both PwcHA and the general population were compiled and grouped as shown in Figure 1.

Figure 1. Methods used to develop the framework for assessing fatalities in PwcHA.

1. Causes of death in PwcHA were compiled from:		
A systematic literature review	The US Food and Drug Administration Adverse Event Reporting System (FAERS) database	Expert c

2. Leading causes of death in the US and worldwide non-hemophilia populations

were sourced from: Centers for Disease Control World Health Organization¹⁰

3. All causes of death were categorized into:

Hemophilia A-associated deaths Non-hemophilia A-associated deaths

4. Causes of death were further grouped into subcategories reflecting the leading causes of death in the non-hemophilia population and those most relevant to PwcHA

5. The mortality framework was assembled for assessing fatalities in PwcHA

PwrHA nersons with connenital hemonhilia A

al Presented at NHF 2020; noster #25.



Results

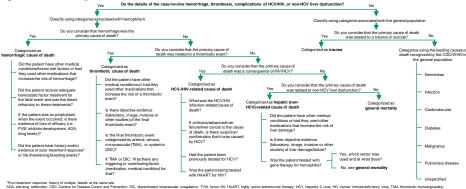
We propose a framework with two main categories: 'HA-associated mortality' and 'non-HA-associated mortality'.

- Based on a systematic literature review11 and Food and Drug Administration Adverse Event Reporting System (FAERS) database analysis,12 we found that PwcHA share mortality causes with the non-hemophilia population; they also retain specific causes associated with complications from hemophilia or its associated treatment.
- . HA-associated mortality causes can be further grouped into four primary categories: hemorrhage, thrombosis, human immunodeficiency virus-/hepatitis C virus (HCV)-related, and hepatic (non-HCV)-related.
- There are then further secondary considerations to enable a more in-depth categorization of complicated cases with multiple reported or contributing causes of death.
- This assessment should be made by the treating physician or healthcare professional, who will have the most in-depth knowledge of each specific case.
- Non-HA-associated mortality causes can first be categorized as traumatic/suicide or non-traumatic/suicide; this allows the user of the framework to easily distinguish between cases which may or may not contribute to meaningful analyses or yield clinical insights relevant to PwcHA.
- Based on information from the Centers for Disease Control and Prevention9 and World Health Organization10 on the leading causes of death in the US and worldwide populations, non-traumatic, non-hemophilia mortality causes can be categorized as: dementias, infection, cardiovascular, diabetes, malignancy, pulmonary disease, and unspecified.
- Cases in which not enough information is available are classed in the 'unspecified' category.

Based on the HA-related and non-HA-related categories, we propose the following framework for the guick and comprehensive categorization of fatalities in PwcHA (Figure 2).

- · Primary considerations determine the main cause of death. Once the user identifies that a given case contains events related to HA or its treatment, an initial categorization is determined
- Secondary considerations help to determine contributing factors to fatalities in PwcHA; for example, for cases of refractory hemorrhage, medically complex cases where the fatality is attributable to multiple causes, and cases where the loss of efficacy of the hemophilia treatment contributed to the fatal event.

Figure 2. Framework for the categorization of death



WHO World Health Omanization



Conclusions







future reporting of these events.



Importantly, this presents a unique opportunity to document the public health impact of innovation in drug development and may reveal positive impacts of the evolving treatment landscape.

Presented at the National Hemophilia Foundation (NHF) Bleeding Disorders Virtual Conference | August 1-8, 2020

1. Medison, et al. 1/16/J Jule ORIGINETHE 1-22, 2- Bust, et al. 1/16/J Jule ORIGINETHE 1-26, 3- Bussio Au et al. Blood 2017 CH 1/18 4: 7- Abrovatory, at al. Heavening DR 1952/3-4, 6 - Tromotive Materiance III Mobile Origination (1961-1964-1964). 6: Plug 1 et al. 1/Tromoti Heavening 2000;4-55/6-7, 7- Deep Ng; et al. Blood 2007/195/6-26, 8- Marracto PR Juper Ogiv Investio Dragos 2007/3-196-9, 2- Control origination (1961-1964-1964). A second origination of the control origination of the control origination of the control origination origination or the control origination origination origination or the control origination origination or the control origination origination origination origination origination origination origination Third-party medical writing support for this poster was provided by Alex Coulthard, BSc, of Gardiner-Caldwell Communications and was funded SMP_Consideration for the organization of the consideration of the consi