Online Resource

Title
Crowdsourcing Sugammadex Adverse Event Rates Using an In-App Survey: Feasibility Assessment From an Observational Study

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Figure A: Number of participants self-reporting (a) years using sugammadex and (b) doses of sugammadex administered per week.

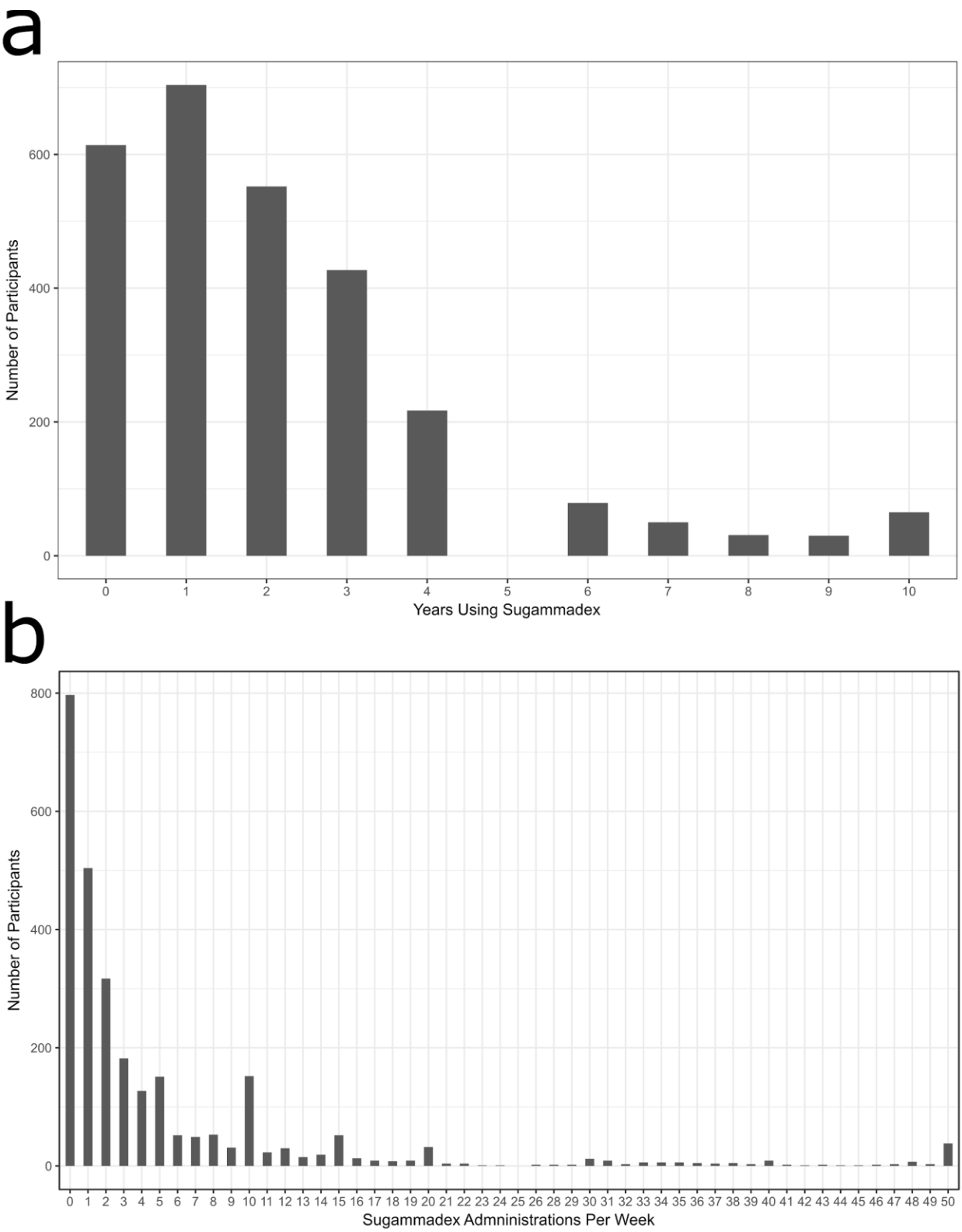

Figure B: Comparison of reporting rate of bradycardia to the rate calculated based on voluntary spontaneous reports of bradycardia reported in the presentation to the FDA Advisory Panel by the manufacturer. Using the same assumptions as those used for anaphylaxis (73 bradycardia events, 10-fold under-reporting, 95% of 11.5 million doses administered), the Clopper-Pearson estimate of the rate of bradycardia compared to our estimate is shown below:

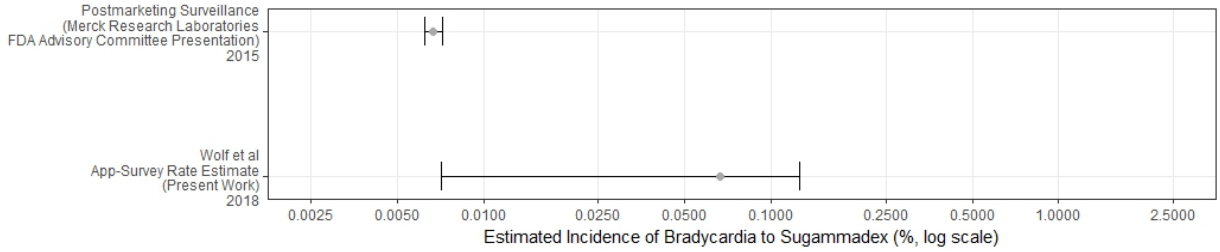

Table A: Branched survey for collection of basic demographic information from users of the app. (NB: "What are is (sic) your practice size?" was the exact verbiage sent in the survey.)

Question	Responses	
About how long have you been using the app (in months)? (Select 0 if you are a new user.)	Range: 0-100	
What is your level of medical training?	Physician: Attending/Consultant	Student Nurse Anesthetist
	Physician: Fellow/Resident/Registrar	Medical Student
	Anesthesia Assistant (PA)	Paramedic/EMT
	Nurse Anesthetist (CRNA)	I am not a medical practictioner
	Nurse (RN)	Respiratory Therapist
	Technically Trained in Anesthesia	Pharmacist
	Anesthesia Technician	Other type of medical provider
	Student AA	
What are your medical specialties?	Anesthesiology	Pediatric Critical Care
	Pain Medicine	Emergency Medicine
	Pediatric Anesthesiology	Pediatrics
	Cardiothoracic Anesthesiology	Internal Medicine
	Obstetric Anesthesiology	Other
	Adult Critical Care	
How many years have you been in practice? (Not counting years in training)	Range: 0-50	
Please rate the importance of the app to your practice:	Not Important At All	
	Of Little Importance	
	Of Average Importance	
	Very Important	
	Absolutely Essential	
I have used the app as a reference under emergent/urgent circumstances:	True/False	
	False	
We would appreciate knowing how the app was useful to you in an emergency:	Free Text Response	
I have used the Society for Pediatric Anesthesia Critical Events Checklist:	True/False	
We would appreciate knowing how the checklist was useful to you:	Free Text Response	
What are is your practice size?	I am the only practitioner for large area	Group 10-25 members
	One of several practitioners in the area	Group 25-50 members
	Group practice 1-5 members	Group > 50 members
	Group 5-10 members	
What is your anesthesia practice model?	Physician only	Physician supervised, no physician on site
	Physician supervised, anesthesiologist on site	No physician supervision
	Physician supervised, non-anesthesiologist physician on site	Not an anesthesia provider
What is your primary practice environment?	Private clinic or office	Small community hospital
	Local health clinic	Large community hospital
	Ambulatory surgery center	Academic department/University hospital
What is community does your practice primarily serve?	Rural	
	Suburban	
	Urban	
I use of the app as a reference for which classes of patients/procedures?	Adult	Regional
	Pediatrics	Pain
	Obstetric	Emergency Room
	Cardiothoracic	Other
	Intensive Care	

Table B: Cumulative ADR reports by geographical region

Region	*Cumulative # Respondents Reporting an ADR*	*Total Number of Respondents*
Australia and New Zealand	2 (6.1%)	33
Caribbean	1 (8.3%)	12
Central America	37 (32.5%)	114
Central Asia	2 (40%)	5
Eastern Africa	10 (40%)	25
Eastern Asia	22 (43.1%)	51
Eastern Europe	63 (30.3%)	208
Middle Africa	0 (0%)	2
Northern Africa	22 (33.3%)	66
Northern America	52 (11.3%)	462
Northern Europe	14 (8.7%)	161
Polynesia	0 (0%)	1
South-Eastern Asia	33 (19.1%)	173
South America	88 (29.7%)	296
Southern Africa	2 (20%)	10
Southern Asia	39 (43.8%)	89
Southern Europe	114 (22.8%)	499
Western Africa	6 (46.2%)	13
Western Asia	60 (31.6%)	190
Western Europe	62 (17.3%)	358

Survalytics Detailed Description

The Survalytics platform is designed to send survey questions to the app and to retrieve survey responses and other analytic metadata from the app. These surveying capabilities are not one-time or static. New survey questions can be delivered via the Internet to the installed base of mobile devices at any time, with the questions being presented to the app users the next time that the app is opened. Survey data and app usage information are transmitted to and from the app utilizing services provided "in the cloud" by Amazon Web Services (Amazon Seattle, WA).

A detailed schema for the survey and analytic data collection was developed. The Survalytics platform allows for the surveys to have a branched structure. Such a branched survey was used to collect basic demographic information from the user after initial installation and agreement by the user to participate in the study. Users had the ability to opt in or opt out of the study at any time.

Location of the device was determined using three different approaches, as described below. For all of the approaches, only the country and "administrative region" were determined and stored, even when more precise determination of location was possible. Here "administrative region" refers to the largest geographical subdivision within the country such as the state in the U.S. or province in India. The precision of the location determination was limited to granularity no more defined than administrative region in order to provide Health Insurance Portability and Accountability Act (HIPAA) compliant de-identification of data. Healthcare providers were entering into the app a patient age and weight. If the location information stored were more precise, patient age and weight information entered into the app might be combined with the specific location and date in a manner that could potentially comprise protected health information (PHI) as defined by HIPAA.

The first of the three approaches to determining the country and administrative region data was based on GPS coordinates which were reverse geocoded using Google's Geocoding API[1]. "Reverse geocoding" refers to the process of converting longitude and latitude coordinates, such as those provided by GPS, into human-interpretable geographic descriptions such as country, state/province, or address. The second approach was based on using the mobile device's Internet Protocol (IP) address. The IP address was reverse geocoded using a web-based service provided by ip-api.com[2]. The last approach was based on the country code stored in the memory chip used to uniquely identify the device (the Subscriber Identity Module or SIM card). Only country information is available via this last approach.

During analysis, the country and administrative region from GPS reverse geocoding was preferentially used. However, GPS coordinates were not always available for a variety of reasons including GPS reception problems, GPS sensor failure, or the device user not consenting to sharing GPS location information. If GPS data were not available, the country and administrative region from IP address was used. Sometimes, this information was not available due to lack of Internet connectivity at the time of data collection. If not, the country from the SIM card (felt to be the least accurate) was used.

The Survalytics platform stores each "event" (e.g. consent, a survey response, an in-app click, or closure of the app) in a local database on the device. When Internet connectivity is detected, one data packet is transmitted from the app at a time, with each packet representing a single "event". Each packet contains relevant details of the event (e.g. what was clicked), as well as a generic set of information including an anonymous globally unique identifier (generated when the app is first opened on the device), time information (specifically, timestamp, time zone, and local time), location information (from the three sources outlined above), and device

language. Transmitted packets are stored as records in an Amazon Web Services DynamoDB database. See the publication describing Survalytics [3] for even further additional technical details.

The anonymous user identifier allows for all of the data from one device to be tied together. Together with the time stamps, this allows the sequence of app usage events and survey responses for each mobile device to be reconstructed from the database.

Mobile Healthcare App Study JSON Document Schema

I. Survey/demographics central database tables

The overall architecture is designed to simplify the codebase by using JSON primarily as a transport vehicle and limiting the number of database fields to those that need to be known by the database in question. For example, the AWS source database for downloading questions only needs to know questionguid (for a hash key) and the json_str containing the meat of the question. Telling it ordinal position simplifies other areas of the Android code and so that was included. Otherwise, the content remains unparsed until downloaded by the Android app.

On device, the database is again limited to guid, ordinal position, and jsonstr. The additional fields are flags for internal tracking use. Parsed JSON supplies fields for the generation of the question on-device and for the uploaded response.

http://www.jsoneditoronline.org/
https://www.guidgenerator.com/online-guid-generator.aspx

On AWS: Question Table:

```
questionguid_str        : STRING, PRIMARY HASH KEY
ordinalposition_int     : INT, RANGE KEY
json_str          : STRING
```

json_str JSON Schema: Question

```
{
        surveyname_str        : STRING
        surveyguid_str: STRING
        ordinalposition_int     : INT
        questionguid_str        : STRING
        questionprompt_str      : STRING
        questiontype_str        : STRING
        responses_arr  : ARRAY
              [
               {
                responseid_int          :INTEGER
                response_str            :STRING
                },
               {
                responseid_int          :INTEGER
                response_str            :STRING
                },
                ....
              ]
OPTIONALLY
        conditional_upon_questionguid_str   : STRING // questionguid to check*
        conditional_upon_responseid_int     : INTEGER // responseid to check*
```

```
                //*-above two work together and both required to be specified

        conditional_upon_datemsid_int       : INTEGER
                // date (in UTC Unix epoch ms) after which to administer this question

        conditionalbycountry_str            : STRING // use ISO 3166 alpha-2 codes

                delaybydays_int                     : INTEGER
                //wait this many days after the question is first downloaded to ask this question

                ongoingquestion_arr                 : ARRAY //array of day of week+time as
follows
                        [
                          {
                         notificationtime_str    : STRING
                          },
                          {
                         notificationtime_str    : STRING
                          },
                         ...
                          //notificationtime formatted as follows:  EEEHHmm
                          // EEE = three letter day of week (Mon, Tue, Wed, Thu, Fri, Sat, Sun,
Dly)
                          //                                          Dly = daily
                          // HH = military time hours 00-23
                          // mm = minutes 00-59
                          //  Examples:      Tue0900, Thu1400, Dly1200
                        ]

                deletequestion_str                  : STRING //questionguid of ongoing
question to
                                                    // delete from local SQLite db

}
```

Local DB on Android

Table questions
questionguid_str
    json_str
ordinalposition_int //Primary key
final_responseid_int
    final_response_str
    answered_bool
    uploaded_bool //unused

Table responses
_id
json
uploaded

II. Responses: Generic schema

The generic schema serves as the basic information passed with all types of uploaded data. The additional overhead is minimal and the presence of this information in each of uploaded packet simplifies future analysis against unnecessary complexity in terms of crossreferences and joins.

```
{
        userguid_str                : STRING        PRIMARY RANGE INDEX
        localtime_ms_int            : INTEGER       PRIMARY HASH INDEX
        localtime_hrsmilitary_int   : INTEGER
        localtime_dayofweek_str     : STRING
        localtimezone_str           : STRING
        country_tm_str                      : STRING
        lo_lang_str                 : STRING        //locale lang
    app_lang_str            : STRING
        region_ipapi_str            : STRING        //www.ip-api.com/json
    regionname_ipapi_str        : STRING
        country_ipapi_str           : STRING
        region_gc_str               : STRING        //geocoding
        country_gc_str              : STRING
        entrytype_str               : STRING        LSI // included in all section III
items
        ...
}
```

III. Responses: Specific added fields to generic document schema

Survey/demographics data

```
…
entrytype_str    : “survey”,
        surveyguid_str          : STRING
        questionguid_str        : STRING
        questionprompt_str      : STRING
        response_str            : STRING
        responseid_str : STRING //questionguid & "-" Integer.toString(respid)
        responses_arr  : ARRAY [if type is multiple response eg checkbox)
                [
                 {
                  responseid_str          :STRING
                                  //questionguid & "-" Integer.toString(respid)
                  response_str            :STRING
                  },
                 {
                  responseid_str          :STRING
                                  //questionguid & "-" Integer.toString(respid)
                  response_str            :STRING
                  },
                  ....
                ]
```

Consent/Consent Change

```
...
entrytype_str           : “consentcode_int/consentchange_int”
“consentcode_int”       : INTEGER
“consentchange_int”     : INTEGER

                          1 - do not consent
                          2 - consent
                          3 - exit study
                          4 - re-enter study
```

On Start

```
...
entrytype_str                   : “onstart”
“age_yrs_fra”                   : FRACTION
“weight_kg_fra”                 : FRACTION
```

Age/weight entered by app user (age over 89 to be reported as 89+)

```
...
entrytype_str                : “ageweight”,
“age_yrs_fra”                : FRACTION
“weight_kg_fra”              : FRACTION
```

Total time using the app

```
...
entrytype_str                : “totaltimeofuse”,
“timeinapp_ms_int”           : INTEGER,
"ageweightmodified_int       : INTEGER //0=no 1=yes
```

Drugs favorited and changes to favorites

```
…
entrytype_str                : “favoriteslist”,
“favoriteslist_arr”          : ARRAY
        [
         {      “drugid_int” : drug.get_id(),          INTEGER
                “name_str”: drug.getDrugName(),  STRING
                “position_int” : favepos                INTEGER
         } ,
         {      “drugid_int” : drug.get_id(),          INTEGER
                “name_str”: drug.getDrugName(),  STRING
                “position_int” : favepos                INTEGER
         } ,
         ....
]
```

In-app clicks (drugs, Epocrates, airway setup guide, critical events checklist, externally linked nerve blocks)

```
...
entrytype_str   :       See the click types below

Entrytype_str click types:
“drugclick”,
“epocrates”,
“linkline_str”,
“airwaysetupguide”

Extra JSON for drug/epocrates
        “drugid_int”                    : drug.get_id()
```

“name_str” : drug.getDrugName()

Extra JSON for linkline:

“linkline_str” : STRING == name //nerveblock and spachecklist

“linklineurl_str” : STRING == link //nerveblock and spachecklist

Methodology for Calculation of Adverse Event Rates

Primary data collected in this calculation were (1) observation of the adverse event by the clinician, (2) the number of administered doses per week estimated by the clinician, and (3) the number of years the clinician has been practicing with sugammadex. The number of events was then based on the number of providers reporting an adverse event using (1) a "low rate" scenario in which providers had only observed the event once, and (2) a "high rate" scenario in which each provider had observed each event 10 times. The total number of doses was determined from the doses given per week and the number of years using sugammadex, using (1) a high-use scenario in which all providers work full-time (46 weeks) and (2) a low-use scenario in which all providers work part-time (26 weeks).

The low rate/high use scenario was used to calculate a low estimate for event rates and the high rate/low use scenario was used to calculate a high estimate for event rates:

(1) Low estimate for adverse event rates (low rate/high use):

$$\frac{\text{Number of Events [number of providers reporting an adverse event] x [low number of observations of that event per provider (=1])}}{\text{Number of Doses [doses of sugammadex used per week] x [total number of years using sugammadex] x [high number of weeks worked per year=46]}}$$

(2) High estimate for adverse event rates (high rate/low use):

$$\frac{\text{Number of Events [number of providers reporting an adverse event] x [high number of observations of event per provider (=10)]}}{\text{Number of Doses [doses of sugammadex used per week] x [total number of years using sugammadex] x [low number of weeks worked per year=26]}}$$

References

1. Google Maps APIs [Internet]. [cited 2016 Jun 19]. Available from: http://www.webcitation.org/6iO62lCZh

2. ip-api Geolocation API [Internet]. [cited 2016 Jun 19]. Available from: http://www.webcitation.org/6iO5uZzHT

3. O'Reilly-Shah V, Mackey S. Survalytics: An Open-Source Cloud-Integrated Experience Sampling, Survey, and Analytics and Metadata Collection Module for Android Operating System Apps. *JMIR Mhealth Uhealth* [Internet] 2016; **4**: e46 Available from: http://dx.doi.org/10.2196/mhealth.5397