表2. AURA\textsuperscript{a}研究期间报告的不良反应

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>MedDRA术语</th>
<th>CIOMS分类/总体频率 (所有CTCAE分级)\textsuperscript{b}</th>
<th>3级或3级以上的CTCAE的频率</th>
</tr>
</thead>
<tbody>
<tr>
<td>呼吸、胸部及纵膈系统疾病</td>
<td>间质性肺病\textsuperscript{c}</td>
<td>常见 (3.2%)\textsuperscript{d}</td>
<td>1.3%</td>
</tr>
<tr>
<td>胃肠道疾病</td>
<td>腹泻</td>
<td>极常见 (44%)</td>
<td>1.0%</td>
</tr>
<tr>
<td>胃肠道疾病</td>
<td>口腔炎</td>
<td>极常见 (15%)</td>
<td>0%</td>
</tr>
<tr>
<td>眼部疾病</td>
<td>角膜炎\textsuperscript{e}</td>
<td>少见 (0.9%)</td>
<td>0%</td>
</tr>
<tr>
<td>皮肤及皮下组织疾病</td>
<td>皮疹\textsuperscript{f}</td>
<td>极常见 (41%)</td>
<td>0.7%</td>
</tr>
<tr>
<td>皮肤及皮下组织疾病</td>
<td>皮肤干燥\textsuperscript{g}</td>
<td>极常见 (29%)</td>
<td>0%</td>
</tr>
<tr>
<td>皮肤及皮下组织疾病</td>
<td>甲沟炎\textsuperscript{h}</td>
<td>极常见 (27%)</td>
<td>0%</td>
</tr>
<tr>
<td>皮肤及皮下组织疾病</td>
<td>瘙痒\textsuperscript{i}</td>
<td>极常见 (15%)</td>
<td>0%</td>
</tr>
<tr>
<td>辅助检查</td>
<td>QTc间期延长\textsuperscript{j}</td>
<td>少见 (0.7%)</td>
<td>0%</td>
</tr>
<tr>
<td>(依据检验结果确定,并按CTCAE级别的变化情况给出)</td>
<td>血小板计数下降\textsuperscript{k}</td>
<td>极常见 (54%)</td>
<td>2.1%</td>
</tr>
<tr>
<td>(依据检验结果确定,并按CTCAE级别的变化情况给出)</td>
<td>白细胞减少\textsuperscript{k}</td>
<td>极常见 (66%)</td>
<td>2.4%</td>
</tr>
<tr>
<td>(依据检验结果确定,并按CTCAE级别的变化情况给出)</td>
<td>中性粒细胞减少\textsuperscript{k}</td>
<td>极常见 (32%)</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 表中所列的数据均为III期(AURA3)和II期(AURAx和AURA 2)研究中累积获得的数据;仅对至少服用了1次本品的患者所发生的不良事件进行了统计。
MedDRA was developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The activities of the MedDRA Maintenance and Support Services Organization (MSSO) are overseen by an ICH MedDRA Management Committee, which is composed of the ICH parties, the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, Health Canada, and the WHO (as Observer).
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Overview

- MedDRA background
- Regulatory Status
- MedDRA’s structure, scope, and characteristics
- MedDRA training and MSSO contacts
MedDRA Background
What is MedDRA?

Med = Medical

D = Dictionary for

R = Regulatory

A = Activities

《监管活动医学词典》
MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.
Where MedDRA is Used

Regulatory Authority and Industry Databases
Individual Case Safety Reports and Safety Summaries

Clinical Study Reports
Investigators’ Brochures
Core Company Safety Information
Marketing Applications
Publications
Prescribing Information
Advertising
MedDRA Users Profile

- As of March 2019
  - ~5,800 Subscribing organizations (MSSO+JMO)
  - 10% increase compared to March 2018
  - 125 Countries
• MedDRA Users by Region

<table>
<thead>
<tr>
<th>Country</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1594</td>
</tr>
<tr>
<td>Japan</td>
<td>793</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>336</td>
</tr>
<tr>
<td>Germany</td>
<td>326</td>
</tr>
<tr>
<td>China</td>
<td>320</td>
</tr>
<tr>
<td>France</td>
<td>249</td>
</tr>
<tr>
<td>Italy</td>
<td>202</td>
</tr>
<tr>
<td>Spain</td>
<td>152</td>
</tr>
<tr>
<td>Canada</td>
<td>129</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>115</td>
</tr>
<tr>
<td>Australia</td>
<td>98</td>
</tr>
<tr>
<td>Netherland</td>
<td>98</td>
</tr>
<tr>
<td>Sweden</td>
<td>97</td>
</tr>
<tr>
<td>India</td>
<td>93</td>
</tr>
<tr>
<td>Switzerland</td>
<td>87</td>
</tr>
</tbody>
</table>
**2019 MedDRA Subscription Rate Table**

<table>
<thead>
<tr>
<th>MedDRA Subscription Types</th>
<th>2019 Annual Subscription Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Authority</td>
<td>$0 USD</td>
</tr>
<tr>
<td>Non-Commercial / Non-Profit</td>
<td>$0 USD</td>
</tr>
<tr>
<td>Commercial (Parent Company Annual Revenue or Turnover)</td>
<td></td>
</tr>
<tr>
<td>Level 0 (Annual Revenue &lt; $1 Million)</td>
<td>$154 USD</td>
</tr>
<tr>
<td>Level 1 (Annual Revenue $1-$10 Million)</td>
<td>$654 USD</td>
</tr>
<tr>
<td>Level 2 (Annual Revenue $10-$20 Million)</td>
<td>$2,496 USD</td>
</tr>
<tr>
<td>Level 3 (Annual Revenue $20-$500 Million)</td>
<td>$4,727 USD</td>
</tr>
<tr>
<td>Level 4 (Annual Revenue $500 Million-$1 Billion)</td>
<td>$9,918 USD</td>
</tr>
<tr>
<td>Level 5 (Annual Revenue $1-$5 Billion)</td>
<td>$41,150 USD</td>
</tr>
<tr>
<td>Level 6 (Annual Revenue $5-$20 Billion)</td>
<td>$54,334 USD</td>
</tr>
<tr>
<td>Level 7 (Annual Revenue &gt; $20 Billion)</td>
<td>$70,889 USD</td>
</tr>
<tr>
<td>System Developer</td>
<td>$2,556 USD</td>
</tr>
</tbody>
</table>

77% of all MedDRA users pay no fee or $654 (or less)
• Subscription grants access to MedDRA for one year
• Subscriber cannot grant any sublicense, publish or otherwise distribute MedDRA to a third party
• Data may be freely exchanged between current MedDRA subscribers
• Sharing MedDRA with a non-subscribing organization is a violation of the MedDRA license
Regulatory Status
Regulatory Status

• FDA, US
  – Used in several databases including FAERS (drugs and biologics), VAERS (vaccines), and CAERS (foods, dietary supplements, cosmetics)
  – Electronic submission required for study data and postmarketing reports (uses ICH standards)

• MHLW/PMDA, Japan
  – Mandatory use in electronic reporting
Regulatory Status (cont)

- EC, Europe
  - EudraVigilance database
    - Clinical trial SUSARs (Suspected Unexpected Serious Adverse Reactions)
    - Post-authorization Individual Case Safety Reports (ICSRs)
    - Requires current version of MedDRA or the one previous to it
  - Good pharmacovigilance practices (GVP) specifically mention MedDRA
  - Used throughout Summary of Product Characteristics (labeling)
Regulatory Status (cont)

• CFDA, China
  – Implementing ICH standards
    • M4 Common Technical Document (February 2018)
    • Clinical trial SUSARs use electronic reporting \[E2B(R3)\] and MedDRA (May 2018)
    • Postmarketing ICSRs may use E2B(R3) and MedDRA (July 2019)
Regulatory Status in China

二、自2018年5月1日起，药物临床研究期间报告严重且非预期的药品不良反应适用《E2A：临床安全数据的管理：快速报告的定义和标准》《M1：监管活动医学词典（MedDRA）》和《E2B（R3）：临床安全数据的管理：个例安全报告传输的数据元素》。

三、自2018年7月1日起，报告上市后药品不良反应适用《E2D：上市后安全数据的管理：快速报告的定义和标准》。

四、自2019年7月1日起，报告上市后药品不良反应可适用《M1：监管活动医学词典（MedDRA）》和《E2B（R3）：临床安全数据的管理：个例安全报告传输的数据元素》的要求。自2022年7月1日起，报告上市后药品不良反应适用以上技术指导原则。
MedDRA Overview
**Scope of MedDRA**

- Medical conditions
- Indications
- Investigations (tests, results)
- Medical and surgical procedures
- Medical, social, family history
- Medication errors
- Product quality issues
- Device-related issues
- Product use issues
- Pharmacogenetic terms
- Toxicologic issues
- Standardized queries

**IN**

- Frequency
  - qualifiers
- Numerical values for results
- Severity descriptors
- Not an equipment, device, diagnostic product dictionary

**OUT**

- Not a drug dictionary
- Patient demographic terms
- Clinical trial study design terms

**Not** a drug dictionary

**Clinical** trial study design terms
Data to be Coded by MedDRA

- Clinical Database
  - Screening
    - I/E Criteria
    - Demography
    - Medical History
    - Baseline Characteristics
  - Therapy
    - Study Drug Administration
    - Concomitant Medication
    - Concomitant Procedures
    - Therapy Compliance
  - Efficacy
    - Base on Protocol
    - Indication
  - Safety
    - Adverse Events
    - Lab Results
    - Vital Signs
    - Reason of Death

MedDRA
ICH E2B (R3) Data Elements in MedDRA

- E2B (R3) - ICSR
- Clinical Trials, Post market

<table>
<thead>
<tr>
<th>Element ID</th>
<th>E2B(R3) Element Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.7.1.r.a.2</td>
<td>Structured Medical History Information (disease / surgical procedure / etc.)</td>
</tr>
<tr>
<td>B.1.8.r.f.2</td>
<td>Indication</td>
</tr>
<tr>
<td>B.1.8.r.g.2</td>
<td>Reaction</td>
</tr>
<tr>
<td>B.1.8.4.b.1</td>
<td>Reported cause(s) of death</td>
</tr>
<tr>
<td>B.1.9.4.r.b.1</td>
<td>Autopsy-determined cause(s) of death</td>
</tr>
<tr>
<td>B.1.10.7.1.r.a.2</td>
<td>Structured information (disease / surgical procedure / etc.) - parent/child report (parent)</td>
</tr>
<tr>
<td>B.1.10.8.r.f.2</td>
<td>Indication - parent/child report (parent)</td>
</tr>
<tr>
<td>B.1.10.8.r.g.2</td>
<td>Reactions (if any and known) - parent/child report (parent)</td>
</tr>
<tr>
<td>B.2.i.1.b</td>
<td>Reaction/event in MedDRA terminology</td>
</tr>
<tr>
<td>B.3.r.c.2</td>
<td>Test Name (MedDRA code)</td>
</tr>
<tr>
<td>B.4.k.7.r.2a</td>
<td>Indication in MedDRA terminology</td>
</tr>
<tr>
<td>B.5.3.r.2</td>
<td>Sender’s diagnosis/syndrome and/or reclassification of reaction/event</td>
</tr>
</tbody>
</table>
System Organ Classes

- Blood and lymphatic system disorders
- Cardiac disorders
- Congenital, familial and genetic disorders
- Ear and labyrinth disorders
  - Endocrine disorders
- Eye disorders
  - Gastrointestinal disorders
  - General disorders and administration site conditions
  - Hepatobiliary disorders
- Immune system disorders
- Infections and infestations
  - Injury, poisoning and procedural complications
- Investigations
  - Metabolism and nutrition disorders
- Musculoskeletal and connective tissue disorders
- Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- Product issues
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
  - Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders
Synonyms, lexical variants, sub-elements

**SOC** = Cardiac disorders

**HLGT** = Cardiac arrhythmias

**HLT** = Rate and rhythm disorders NEC

**PT** = Arrhythmia

**LLT** = Dysrhythmias

**LLT** = Other specified cardiac dysrhythmias

**LLT** (Non-current) = Other specified cardiac dysrhythmias

**LLT** = Arrhythmia

**LLT** = Arrhythmia

**LLT** = Arrhythmia NOS

Not all LLTs shown
• Retrieve cases with MedDRA Hierarchy
Primary SOC Graphical Display Example

The graph shows the relative frequency of events categorized under various System Organ Classifications (SOCs). The x-axis represents the relative frequency of any event, and the y-axis lists different SOC categories. The bars indicate the percentage of events for each SOC.

- Ear: 1.9%
- Eye: 1.3%
- Gastr: 13.2%
- Genit: 3.7%
- Immun: 0.3%
- Infec: 12.8%
- Inj&P: 1.5%
- Inv: 3.0%
- Metab: 1.5%
- Musc: 1.9%
- Nerv: 10.7%
- Preg: 0.3%
- Psych: 0.6%
- Repro: 1.5%
- Resp: 8.8%
- Skin: 3.0%
- Surg: 0.9%
Primary SOC Output

Listing Example

SOC Nervous system disorders

8

HLGT Mental impairment disorders

- HLT Mental impairment (excl dementia and memory loss)
  - PT Disturbance in attention 1

HLGT Movement disorders (incl Parkinsonism)

- HLT Dyskinesias and movement disorders NEC
  - PT Psychomotor hyperactivity 2
- HLT Tremor (excl congenital)
  - PT Tremor 3

HLGT Neurological disorders NEC

- HLT Disturbances in consciousness NEC
  - PT Somnolence 1
- HLT Neurological signs and symptoms NEC
  - PT Dizziness 1
Standardised MedDRA Queries (SMQs)
Standardised MedDRA Queries (SMQs)

- Collaboration between CIOMS (Council for International Organizations of Medical Sciences) and ICH (MSSO)
- Groupings of terms from one or more MedDRA SOCs related to medical condition or area of interest
- Terms relate to signs/symptoms, diagnoses, syndromes, physical findings, laboratory and other test data, etc.
- Intended to aid in case identification
How to “Run” SMQs (cont)
SMQs in Production - Examples

- As of Version 22.0, a total of 104 level 1 SMQs in production

- Agranulocytosis
- Anaphylactic reaction
- Cerebrovascular disorders
- Convulsions
- Depression and suicide/self-injury
- Hepatic disorders
- Hypersensitivity
- Ischaemic heart disease
- Lack of efficacy/effect
- Medication errors
- Osteonecrosis
- Peripheral neuropathy
- Pregnancy and neonatal topics
- Pseudomembranous colitis
- Rhabdomyolysis/myopathy
- Severe cutaneous adverse reactions
- Systemic lupus erythematosus
SMQ Applications

• Clinical trials
  – Where safety profile is not fully established, use multiple SMQs on routine basis as screening tool
  – Selected SMQs to evaluate previously identified issue (pre-clinical data or class effect)

• Post-marketing
  – Selected SMQs to retrieve cases for suspected or known safety issue
  – Signal detection (multiple SMQs employed)
  – Single case alerts
  – Periodic reporting (aggregate cases for safety and other issues, e.g., lack of efficacy)
MedDRA Tools and Training
IT Considerations

• Software tools support the use of MedDRA
  – Several are free with MedDRA subscription
    • Three browsers (Desktop, Web-Based, Mobile)
    • MedDRA Version Analysis Tool (MVAT)
  – Software tools need driven by the volume of data
    • With small amounts, users can use simple software
tools (e.g., free MSSO browsers, spreadsheets)
    • Larger implementations may need commercial data
management products
• List of third-party software tools on MedDRA website
MedDRA Training Opportunities – Available for Users

• Free Face-to-Face (F2F) training
  – Coding with MedDRA
  – Safety Data Analysis and Standardised MedDRA Queries
  – Getting Started with MedDRA

• Free webinars
  – Getting Started with MedDRA
  – MedDRA Overview
  – MedDRA Coding Basics
  – Advanced MedDRA Coding
  – Data Analysis and Query Building with MedDRA
  – Standardised MedDRA Queries
  – What’s New with MedDRA (with each MedDRA release)
MedDRA Training Opportunities – Available to All

• Free resources on MedDRA website
  – Slides for all F2F courses and webinars
  – Short videocasts on MedDRA-related topics
    • Available in several languages
    • Can be downloaded or viewed directly on website
    • Help trainees prepare for F2F courses
• Webinars and videocasts available on new MedDRA MSSO YouTube Channel
More Resources for MedDRA Users

- MedDRA website
  - Help Desk
  - Subscriptions
  - News and Events
  - MedDRA Best Practices document
  - Points to Consider documents
  - Terminology downloads
  - Training
  - Tools
  - MedDRA publications
  - User group meetings
  - Expert meetings
MSSO Contacts

- Website
  - www.meddra.org
- Email
  - mssohelp@meddra.org
- Frequently Asked Questions
  - www.meddra.org/faq