Biologics and Biosimilars Collective Intelligence Consortium (BBCIC)

March 23, 2016

Post-market Examination of Biosimilars & Novel Biologics:

The BBCIC 2016 Surveillance Plan

BBCIC
Biologics & Biosimilars
Collective Intelligence Consortium

Agenda

- Managed Care and Advancing Surveillance Science for the Public Good: The BBCIC strategy
  - Why the BBCIC Is Needed. Active Surveillance
  - Progress to Date
  - 2016 Research Scope
  - Governance structure & participants
- BBCIC Foundations: Distributed Research Networks (DRN)
  - DRN Surveillance Examples
  - DRN Research Methods
  - DRN Processes (Mini-Sentinel Example)

With thanks to the founding Participants of the BBCIC:

AbbVie • Amgen • Anthem-Healthcore • Boehringer Ingelheim Pharmaceuticals, Inc. • Express Scripts • Group Health Cooperative • Harvard Pilgrim Health Plan • HealthPartners •Hematology Oncology Pharmacy Association (HOPA) • Henry Ford Health Systems • Merck • Momenta Pharmaceuticals, Inc • Pfizer Inc.

Introducing Our Oldest & Newest BBCIC Members

abbvie

Jerry Clewell, Pharm.D. MBA
US Scientific Director, Biotherapeutics Strategy, AbbVie

MOMENTA

Paul Miller, Senior Director of Medical Affairs and Communications
Momenta Pharmaceuticals, Inc.

HOPA
Hematology/Oncology Pharmacy Association

Sarah Scarpace, PharmD, MPH, BCOP
President Elect, HOPA

BBCIC Purpose: Why the BBCIC is Needed

- Biosimilars represent an important scientific advancement
- Currently there is no *Active* post-approval evidence generation system in the US for monitoring biologics and biosimilars.
- Physicians, patients and other stakeholders will have questions about the safety and effectiveness of biosimilars, similar to what was experienced with the introduction of generics more than a generation ago. Anecdotal reporting is often the public's only source of information and can misinform.
- This is an important public health need that managed care stakeholders have the capacity and infrastructure to address.
- Our managed care data infrastructure allows the BBCIC to **actively monitor biosimilars and their innovator products, using anonymous data across more than 100 million patients.**

BBCIC Overview

- BBCIC is the **neutral convener** of managed care organizations (MCOs), integrated delivery networks (IDNs), pharmacy benefit managers (PBMs), biopharmaceutical companies, researchers, physicians and patient advocates, and non-profit membership organizations.
- The BBCIC will use **data and analytic methods that have been well tested** to help ensure we have the ability to evaluate any issues concerning biologics and biosimilars. This improves the efficiency and cost-effectiveness of post-marketed RWE.
- The BBCIC will use a ***transparent organized process*** to characterize patient populations and generate evidence for biologics in a manner that promotes robust relevant scientific research and exchange.
- This multi-stakeholder consortium model allows for a larger voice with **more credibility**. By bringing together a broad coalition of stakeholders, the consortium also will be able to prioritize and address data challenges.

BBCIC Progress To Date

- An AMCP task force recommended establishing a multi-stakeholder consortium for biologics & biosimilars post-approval evidence generation.
  - The task force included MCOs, IDNs, PBMs, Pharma & Research Institutions
- Feasibility study and business plan completed in 2014
- BBCIC officially kicked off in April 2015
  - 15 founding participants including managed care and integrated delivery organizations, PBMs, research institutions and pharmaceutical companies
  - 6 month organizing phase finished December 2015 (charter, policy & research plan, signed contracts)
  - Research protocol development started January 2016
- Research commences Q2 2016

2016 Research Scope

In 2016, the BBCIC will focus on biologics for which biosimilars are anticipated in the 2016-2018 timeframe

- ❑ Descriptive Analyses
  - G-CSFs, Infliximab, Epoetin Alfa, Insulin glargine and lispro, rituximab, adalimumab, abciximab, cetuximab, palivizumab, trastuzumab
- ❑ Comparative Safety and Effectiveness Research
  - G-CSF Agents (Including Neupogen, Neulasta, TBO-filgrastim, filgrastim and pegfilgrastim biosimilars)
- ❑ Process:
  - BBCIC Participants submit topics (i.e., key questions of interest) for the Annual Research Plan
  - Quarterly update process for Annual Research Plan

Draft 2016 Research Scope—Another View

Biologic/Biosimilar Product	Disease Indications
G-CSF Agents (Neupogen, Neulasta, TBO-filgrastim, Zarxio)	Febrile Neutropenia risk reduction in non-myeloid malignancies treated with myelosuppressive anti-cancer drugs associated with a febrile neutropenia.
Adalimumab (Humira), infliximab (Remicade), rituximab (Rituxan), and optional tocilizumab (Actemra), abatacept (Orencia), etanercept (Enbrel), certolizumab (Cimzia), golimumab (Simponi), ustekinumab (Stelara), secukinumab (Cosentyx), tofacitinib (Xeljanz)	RA, JRA, Psoriasis, PsA, Ankylosing Spond, SJIA, PJIA
Adalimumab (Humira), infliximab (Remicade), and optional: certolizumab (Cimzia), natalizumab (Tysabri), golimumab (Simponi)	Ulcerative Colitis, Crohn's Disease
Insulin glargine (Lantus, Toujeo), insulin lispro (Humalog), and optional: insulin determir (Levemir), insulin degludec (Ryzodec, Tresiba), insulin degludec+liraglutide (Xultophy)	Diabetes Mellitus 1 and 2
Epoetin alfa (Epogen, Procrit) and optional darbepoetin alfa (Aranesp), methoxy polyethylene glycol-epoetin beta (Mircera)	Anemia (CKD)
Palivizumab (Synagis)	Respiratory Syncytial Virus (RSV)
Rituximab (Rituxan)	NHL, CLL, WG/MPA
Abciximab (Reopro)	adjunct PCI (percutaneous coronary intervention), unstable angina
Trastuzumab (Herceptin)	Adjuvant HER2-Breast Cancer; Metastatic HER2-Breast Cancer; Metastatic HER2- Gastric Cancer

2016 Research Scope: G-CSFs Research Team

- We propose a descriptive analysis to characterize first-cycle high neutropenia risk chemotherapy in patients with breast or lung cancer or lymphoma treated with use of G-CSFs
- Completing this assessment phase--describing key clinical data elements, relevant populations and potential confounders will lead us into the next research protocol where we will launch a RWE comparative safety and effectiveness study of G-CSFs

Vanita Pindolia, PharmD, VP, Ambulatory Clinical Pharmacy Programs, Henry Ford Health System
Co-Principal Investigator, BBCIC G-CSF Research Team

2016 Research Scope: Insulins Research Team

- Our Insulins descriptive analysis will characterize the patient factors predictive of diabetes response (i.e., reduction in A1C levels) and hypoglycemic episodes in diabetic adults.
- This analysis will inform the subsequent development of an observational comparative safety and effectiveness study of insulin biosimilars and innovators in diabetics.
- The analyses focus on determining the availability of key data elements, describing relevant populations, and identifying potential confounders.

Cheryl N. McMahill-Walraven, PhD, Informatics Manager Aetna, Principal Investigator, BBCIC Insulins Research Team

2016 Research Scope: Anti-Inflammatories

- We will study hospitalized infection rates for the anti-inflammatories in patients with rheumatoid arthritis , psoriatic and GI conditions.
- This will allow us to build a test case within the AMCP-BBCIC data environment that will be transferable to biosimilars when they hit the market.
- We will focus on describing key data elements, relevant populations and confounders.
- We will consider whether existing algorithms to capture serious infections and other covariates need adjustment.

Kevin Haynes, PharmD, MSCE, Director of Clinical Epidemiology, Healthcore
Principal Investigator, BBCIC Anti-Inflammatory Research Team

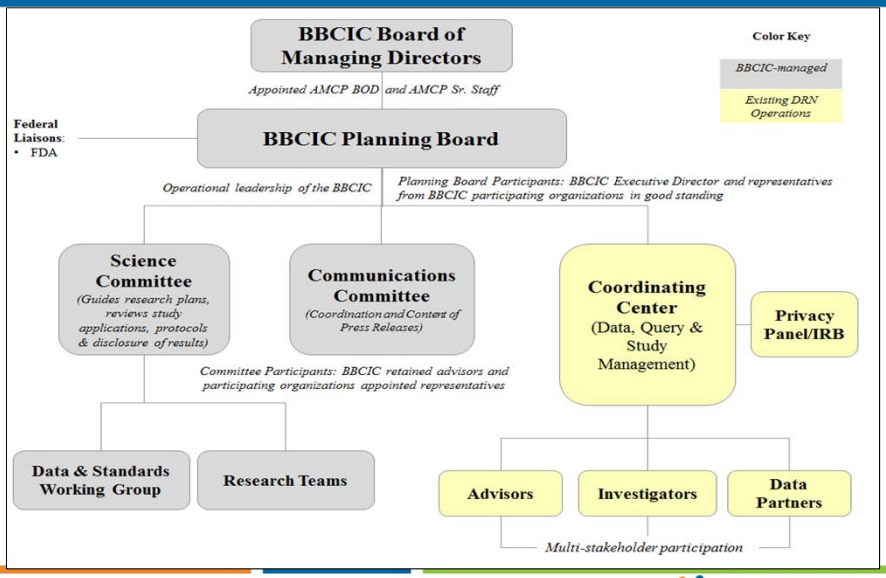
2016 Research Scope: ESAs Research Team

- The Erythropoietin Stimulating Agents (ESA) research team will conduct a descriptive analysis of ESA treatment patterns across the US dialysis centers.
- The specific research questions of interest for this descriptive study include understanding facility characteristics, patient clinical characteristic, and dosing patterns and associated haemoglobin response
- This analysis is to prepare for a comparative effectiveness study of innovator and biosimilar ESAs.

Cathy Panozzo, MPH, PhD, Instructor, Harvard Medical School/Harvard Pilgrim Health Care Institute
Co-Principal Investigator, BBCIC ESA Research Team

Pam Pawloski, PharmD, Research Investigator, HealthPartners Institute for Education and Research
Co-Principal Investigator, BBCIC ESA Research Team

BBCIC Governance Overview



Speaker

Jeffrey Brown, PhD

Associate Professor, Department of Population Medicine (DPM) at Harvard Medical School and the Harvard Pilgrim Health Care Institute

- ***BBCIC Foundations: Distributed Research Networks (DRN)***
  - DRN Surveillance Examples
  - DRN Research Methods
  - DRN Processes (Mini-Sentinel Example)

BBCIC: Capitalizing on Investments

Some distributed networks

- CDC's Vaccine Safety Datalink (VSD)
- HMO Research Network
- Cancer Research Network
- Meningococcal Vaccine Safety Study
- EU-ADR
- FDA Mini-Sentinel
- NIH Health Care Systems Collaboratory
- PCORI National Clinical Research Network (PCORnet)

BBCIC –FDA's Next Generation Surveillance

At the 2015 Sentinel Public Workshop, FDA signaled:

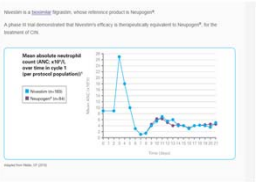
Janet Woodcock, FDA Director CDER:

- "Through Mini-Sentinel we've shown we can obtain rapid responses to [safety] signals – these questions that arise after marketing and get everyone in a twist …"
- We're going to transfer Sentinel to our safety office so we can **institutionalize the use of Sentinel as part of our safety tool kit.** As we see a problem – and the OSE is dealing with a myriad of safety signals at any given time – this is one of the tools they can easily reach for."

Michael Nguyen, FDA Center for Biologics Evaluation & Research

- BBCIC-type effort "Substantially expands postmarket safety monitoring options to allow more strategic and tailored surveillance of new drugs and biologics"
- FDA Advisory Committees are likely to look favorably on surveillance plans that include Sentinel level (e.g., BBCIC) active prospective surveillance.
- FDA Post-Approval Committees (PAC)s will be looking for "near real-time active surveillance for prespecified outcomes"
- FDA is "Working to apply Sentinel to all classes of CBER-regulated products

http://www.brookings.edu/events/2015/02/05-fda-sentinel-initiative-workshop



DRNs: Assessing Risk

Active Surveillance of Vaccine Safety

A System to Detect Early Signs of Adverse Events

Robert L. Davis,[†] Margarette Kolczak,[‡] Edwin Lewis,[†] James Nordin,[§] Michael Goodman,[§] David K. Shay,[‡] Richard Platt,[¶] Steven Black,[†] Henry Shinefield,[†] and Robert T. Chen[‡]*

Background: There currently are no population-based systems in the United States to rapidly detect adverse events after newly introduced vaccines. To evaluate the feasibility of developing such systems, we used 5 years of data from 4 health maintenance organizations within the Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink.

Methods: Within every year, each week's vaccinated children were followed for 4 weeks, and rates of adverse events were compared with rates among children of similar ages before the introduction of the new vaccine. We assessed risks for intussusception after rotavi-

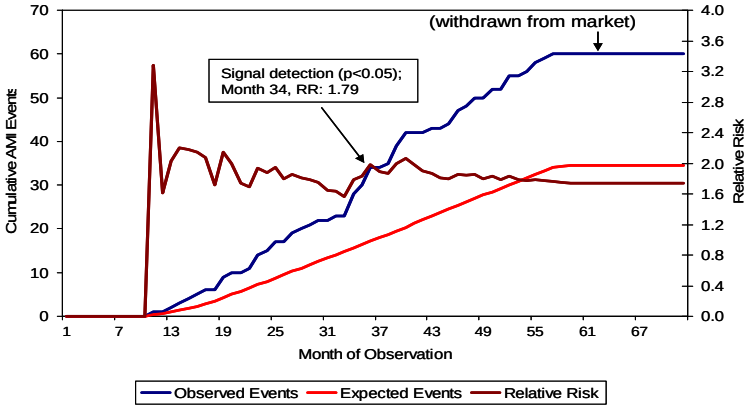
Conclusions: We conclude that it is feasible to develop systems for rapid and routine population-based assessments of new vaccine safety.

(*Epidemiology* 2005;16: 336–341)

Recent events in the United States have underscored the need for surveillance systems that detect adverse events as soon as possible after the introduction of new vaccines (eg,

DRNs: Assessing Risk

Observed and expected events for rofecoxib versus naproxen users: 2000-2005

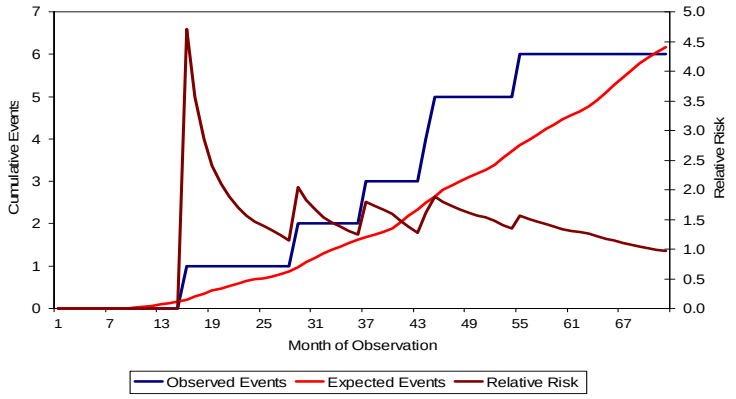


Signal after 28 events (16 expected) among new users of drug

Brown *et al*. (2007) PDS; Adjusted for age, sex, health plan. Outcome: AMI.

DRNs: Assessing Risk

Observed and expected events for cetirizine users versus non-users: 2000-2005



Negative control;6 observed and 6.1 expected. > 5 million exposed days.

Brown *et al*. (2007) PDS; Adjusted for age, sex, health plan. Outcome: Thrombocytopenia.

DRNs: Assessing Risk

Dabigatran and Post-Marketing Reports of Bleeding

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

* Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were enrolled in plans for drug and medical coverage and had been given a diagnosis of atrial fibrillation in any care setting. Patients were excluded from the cohorts if, in the 183 days before the index dispensing, they had a claim for an event of interest in an inpatient or emergency department setting or a claim for dispensing of dabigatran or warfarin. Events were assessed during drug exposure, from inpatient or emergency department settings only.

N ENGL J MED 368;14 NEJM.ORG APRIL 4, 2013

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DRNs: Assessing Risk

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 6, 2014 VOL. 370 NO. 6

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

W. Katherine Yih, Ph.D., M.P.H., Tracy A. Lieu, M.D., M.P.H., Martin Kulldorff, Ph.D., David Martin, M.D., M.P.H., Cheryl N. McMahill-Walraven, M.S.W., Ph.D., Richard Platt, M.D., Nandini Selvam, Ph.D., M.P.H., Mano Selvan, Ph.D., Grace M. Lee, M.D., M.P.H., and Michael Nguyen, M.D.

ABSTRACT

BACKGROUND

International postlicensure studies have identified an increased risk of intussuscep-

From the Department of Population

CONCLUSIONS

RV5 was associated with approximately 1.5 (95% CI, 0.2 to 3.2) excess cases of intussusception per 100,000 recipients of the first dose. The secondary analysis of RV1 suggested a potential risk, although the study of RV1 was underpowered. These risks must be considered in light of the demonstrated benefits of rotavirus vaccination. (Funded by the Food and Drug Administration.)

Distributed Research Networks: Methods

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 1275–1284
Published online 22 October 2007 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1509

ORIGINAL REPORT

Early detection of adverse drug events within population-based health networks: application of sequential testing methods[†,‡]

Jeffrey S. Brown PhD[1,2*], Martin Kulldorff PhD[1], K. Arnold Chan MD, MPH, ScD[3,4], Robert L. Davis MD, MPH[5], David Graham MD[6], Parker T. Pettus MS[1,2], Susan E. Andrade ScD[2,7], Marsha A. Raebel PharmD[2,8], Lisa Herrinton PhD[2,9], Douglas Roblin PhD[2,10], Denise Boudreau PhD[2,11], David Smith PhD[2,12], Jerry H. Gurwitz MD[2,7], Margaret J. Gunter PhD[2,13] and Richard Platt MD, MSc[1,2]

Distributed Research Networks: Methods

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3412

ORIGINAL REPORT

Near real-time adverse drug reaction surveillance within population-based health networks: methodology considerations for data accrual†

Taliser R. Avery[1,2]*, Martin Kulldorff[1,2], Yury Vilk[1], Lingling Li[1], T. Craig Cheetham[2,3], Sascha Dublin[2,4], Robert L. Davis[2,6], Liyan Liu[2,5], Lisa Herrinton[2,5] and Jeffrey S. Brown[1,2]

Purpose: Practical considerations for implementation of real-time drug safety surveillance using safety of generic versus branded divalproex as use case

Methods: Near real time surveillance at 4 health plans; monthly data extracts

Results: Data quality review process for each extract at each site is crucial. Data lags exists but can be accounted for.

Conclusions: Near real-time sequential safety surveillance is feasible, but several barriers warrant attention. …differential accrual between exposure and outcomes could bias risk estimates towards the null, causing failure to detect a signal.

Distributed Research Networks: Methods

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2009; 18: 226–234
Published online 15 January 2009 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/pds.1706

ORIGINAL REPORT

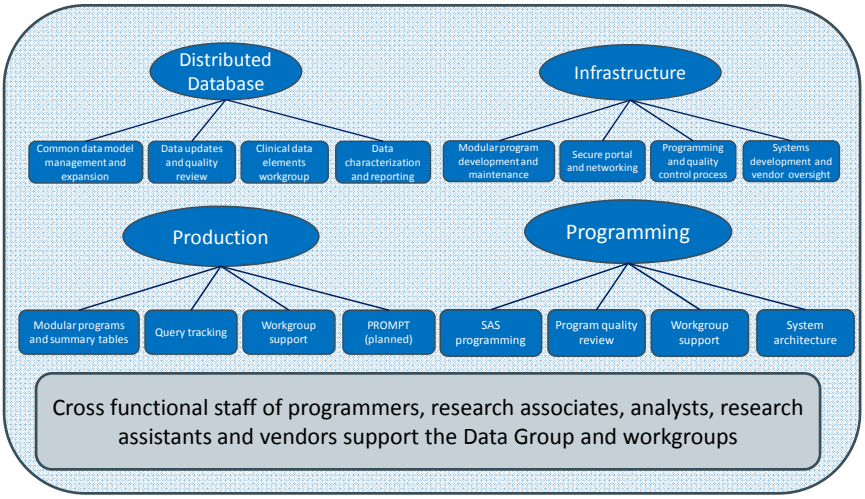
Early adverse drug event signal detection within population-based health networks using sequential methods: key methodologic considerations†

Jeffrey S. Brown PhD[1,2]*, Martin Kulldorff PhD[1], Kenneth R. Petronis PhD[3], Robert Reynolds ScD[3], K. Arnold Chan MD, MPH, ScD[4,5], Robert L. Davis MD, MPH[6], David Graham MD[7], Susan E Andrade ScD[2,8], Marsha A. Raebel PharmD[2,9], Lisa Herrinton PhD[2,10], Douglas Roblin PhD[2,6], Denise Boudreau PhD[2,11], David Smith PhD[2,12], Jerry H. Gurwitz MD[2,8], Margaret J. Gunter PhD[2,13] and Richard Platt MD, MSc[1,2]

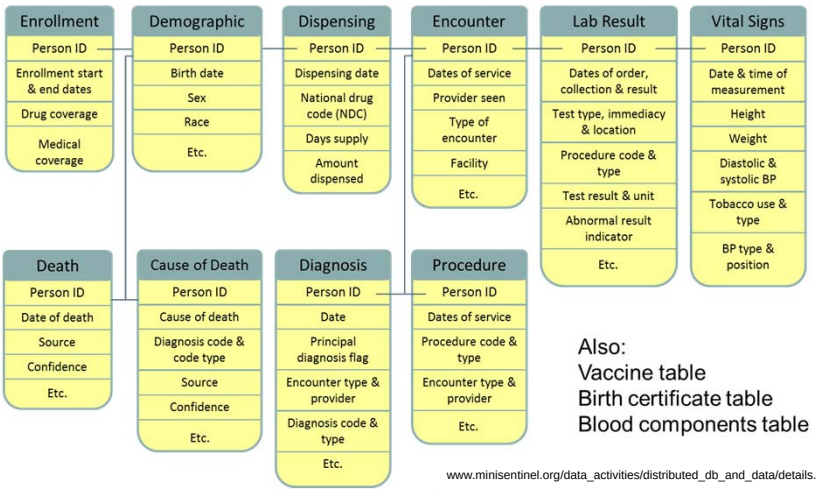
…alternative specifications tend to result in earlier signal detection by 10–16 months, a likely consequence of more exposures and events entering the analysis.

DRN Process: Mini-Sentinel Coordinating Center

Scientific and technical infrastructure



DRN : Mini-Sentinel's Common Data Model



Also:
Vaccine table
Birth certificate table
Blood components table

www.minisentinel.org/data_activities/distributed_db_and_data/details.aspx?ID=105

Questions?

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Email comments and questions to Bernadette Eichelberger, beichelberger@BBCIC.org

BBCIC Contacts

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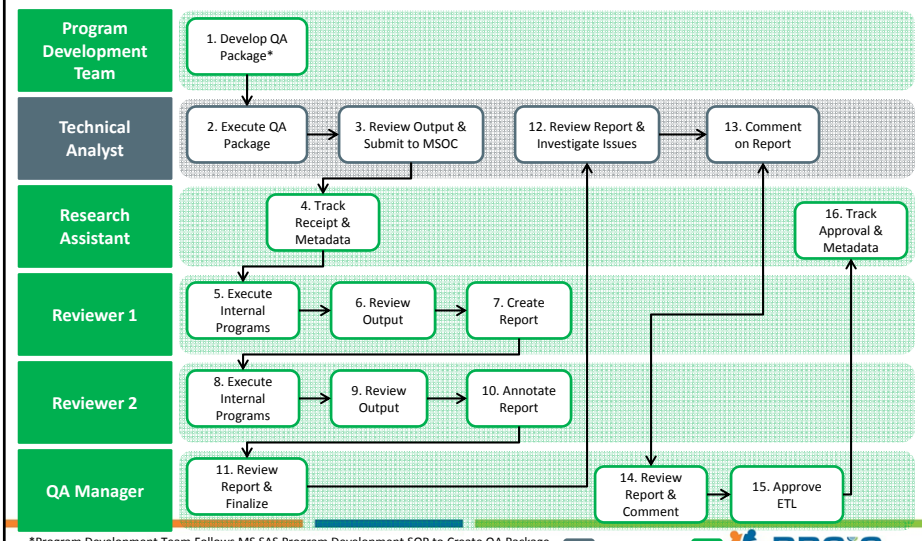
Appendix: DRN Processes

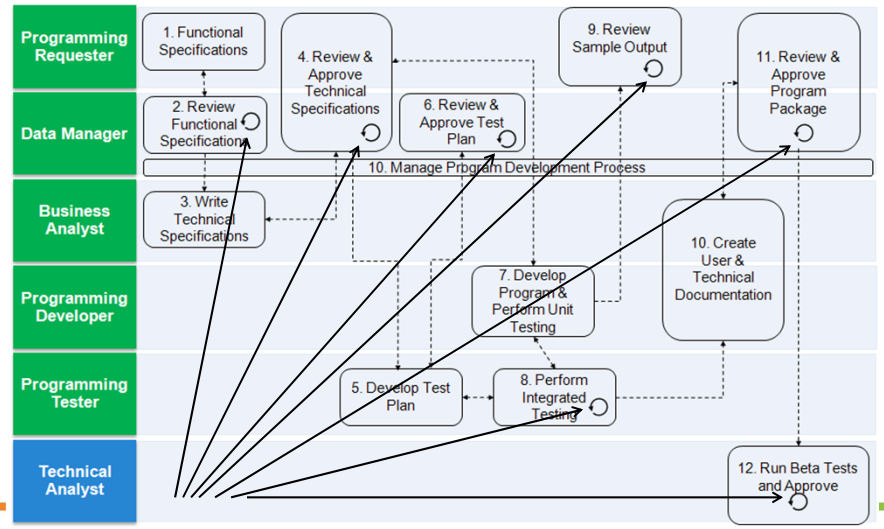
DRN Process : Data QA and Characterization



*Program Development Team Follows MS SAS Program Development SOP to Create QA Package

Data Partner MSOC

DRN Process : New Program Development



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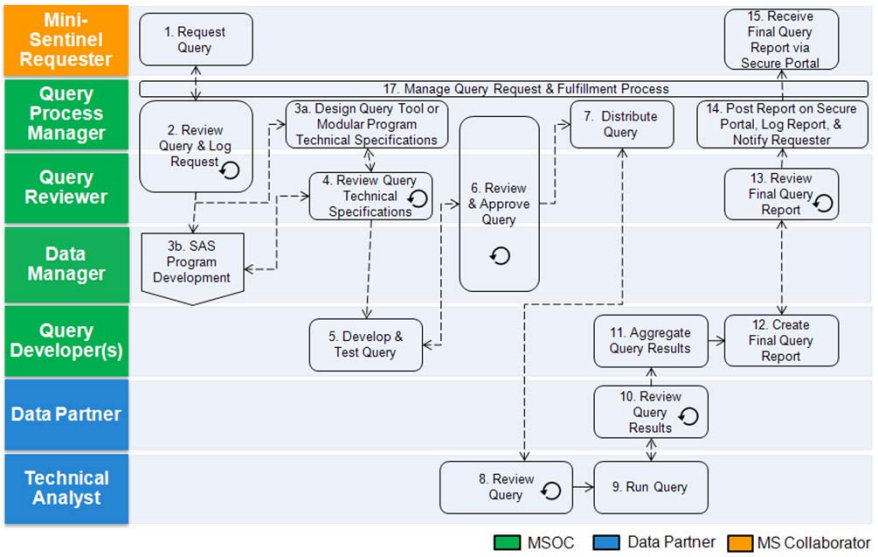
DRN Process: Query Fulfillment



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