

I. Implementing the COMBINE Trial Results in the ImproveCareNow (ICN) Learning Health Network

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II. Executive Summary

The goal of this proposal is to improve the care and outcomes of pediatric patients with Crohn's Disease (CD) by disseminating and implementing the results of the COMBINE trial [1] within the ImproveCareNow Learning Health Network. It aims to integrate the findings into clinical care by promoting combination therapy with tumor necrosis factor inhibitor (TNFi) adalimumab (ADA) and discontinuing it for infliximab (IFX) at drug initiation.

ICN's existing Learning Health Network infrastructure, including improvement and implementation science expertise, strong engagement from patients, families, clinicians, and researchers, and its registry and analytic capabilities, will accelerate the implementation of COMBINE's findings across pediatric GI practice in an equitable and reliable manner.

The desired outcomes of the project are:

1. Increase awareness and motivation to change care across the ICN community based on the COMBINE results.
2. Increase adoption and implementation of the findings in clinical practice.
3. Improve the effectiveness of TNFi therapy in achieving remission.
4. Maintain the adoption and implementation of these changes over time.

The need being addressed by this project lies in the clear result provided by the COMBINE trial that will significantly impact treatment decisions for pediatric patients with moderate to severe Crohn's Disease. Current published guidelines recommend combination therapy with an immunomodulator, low-dose methotrexate (MTX), for adults and for pediatric patients on IFX, but monotherapy for children on ADA. Without a systematic approach to implementation, we will not optimize treatment for patients starting on ADA, nor avoid exposure to unnecessary medication for patients starting on IFX.

The COMBINE study addressed a critical knowledge gap for thousands of pediatric patients initiating TNFi therapy, identifying those who will benefit from combination therapy and those who can avoid it. With its large community of care centers, clinicians, researchers, and families, covering about 60% of all pediatric IBD patients and pediatric gastroenterologists, ICN is uniquely positioned to ensure that the findings can be applied quickly and equitably.

The project has three aims:

Aim 1: Engage the ICN community to understand the information needs, practice settings, and barriers to implementation to design an effective dissemination and implementation plan and resources.

Aim 2: Disseminate broadly across the ICN Network, test and refine a context-specific implementation plan in a subgroup of care centers.

Aim 3: Scale up implementation activities to the entire ICN network while establishing an iterative learning loop for ongoing optimization to accelerate adoption.

The project will lead to updated community-developed care guidelines, dissemination materials, shared decision-making tools, an implementation plan, and a knowledge repository. Implementation will be tested in a subgroup of care centers before scaling across the entire ICN network. Continuous evaluation and optimization of interventions will be supported by feedback from the community.

The project has the potential to impact the outcomes and quality of life of thousands of children with Crohn's Disease across the country year after year. It will address equitable implementation of the results for patients and families. It will set an example of how better systems for organizing healthcare can sharply reduce delays between evidence generation and application in healthcare.

III. Project Goal / Strategy / Outcomes / Need

Project Goal: Improve the care and outcomes of patients with pediatric Crohn's Disease by disseminating and implementing COMBINE trial results across the ImproveCareNow Network of > 100 GI centers and 35,000 patients. We will integrate findings into clinical care, promoting combination therapy for adalimumab and discontinuing it for Infliximab at initiation.

Strategy: We will leverage ICN's existing learning health network structure, resources, and high levels of patient, family, clinician, and researcher engagement to disseminate and implement the COMBINE results by taking advantage of the network's capabilities in improvement and implementation science, as well as its registry and analytic capabilities.

Outcomes: We intend to: 1) increase awareness of the COMBINE results and motivation to change care accordingly, across the ICN community, 2) increase adoption and implementation of findings, 3) increase the effectiveness of TNFi therapy on remission, and 4) maintain the adoption and implementation of these changes over time.

Need/Problem being addressed by the proposed project: COMBINE provided a clear result that will alter care. AGA guidelines for adults recommend anti-TNF combination therapy with MTX over monotherapy [2], and pediatric ECCO/ESPGHAN guidelines [3] recommend combination therapy for IFX but not necessarily with ADA. Without a systematic approach to implementation, we will not optimize treatment for patients starting ADA nor avoid exposure to unnecessary medication for patients starting IFX.

IV. Significance/Impact

Significance: The COMBINE findings closed a critical gap in knowledge for thousands of pediatric patients starting TNFi therapy, whether to use combination therapy with an immunomodulator. The findings represent a shift that will affect decision-making by identifying patients who stand to benefit from combination therapy and those who can avoid it. These results could have significant, immediate implications for managing pediatric CD, but only if they are disseminated and implemented into practice. ICN is uniquely positioned to shorten the time between the publication of clinical trial results and their positive, equitable impact on the health and well-being of children and youth. The network includes all patients at each of ICN's 100 pediatric gastroenterology care centers in the US (comprising about 60% of all pediatric IBD patients and pediatric gastroenterologists), a community of clinicians, researchers, and families, and robust infrastructure for dissemination and implementation (D&I). The network's community and infrastructure - communication capability, training, tools, and coaching for collaborative QI and practice change, registry with data collected at each clinic visit and clinical decision support tools, analytic capability to measure processes and outcomes of care, and transparent sharing of performance across centers - will provide the foundation for D&I, ongoing optimization, as well as the development of new knowledge.

Impact: Implementing the COMBINE results across ICN has the potential to reach the majority of the children in the country with Crohn's disease, improving outcomes and quality of life of thousands of children year after year. As of May 2023, 8,829 patients with CD (<21 years, and > 20 kg) enrolled in ICN were on TNFi therapy, and approximately 1,500 new patients start TNFi therapy annually. ICN's infrastructure also has the capability of implementing new findings equitably by designing, testing, and scaling D&I approaches to meet the needs of socially disadvantaged patients and families. Beyond ICN, this initiative has the potential to demonstrate how to significantly reduce the unacceptable delays between evidence generation and application in practice while building knowledge and experience relevant across healthcare.

V. Hypothesis and Specific Aims

Hypothesis: Our central hypothesis is that by integrating dissemination, improvement, and implementation science methods in a Learning Health Network, we will accelerate the reliable implementation of evidence from the COMBINE study into widespread pediatric GI practice. We will pursue the following three aims:

Aim 1: Engage the ICN community to understand the information needs, practice settings, and barriers to implementation to support the design and development of a D&I plan and resources (9 months)

Rationale: Understanding the information needs, practice settings, and barriers to implementation are necessary to design and develop an effective plan, resources, and evaluation approach to disseminating and implementing the COMBINE findings into practice.

Overall strategy and methods: We will take advantage of the insights and expertise of the ICN community to design and develop an integrated dissemination and implementation (D&I) plan. The dissemination plan will consist of strategies aimed at bolstering awareness and understanding of the COMBINE findings and motivating their use. Data from this plan will be used to create and adapt implementation strategies supporting context-specific implementation at GI centers across the network. Design and development activities will include: engaging clinician, patient, and caregiver stakeholders via existing network structures (e.g., webinars, community meetings) to understand participants' perspectives, perceived barriers to adoption, and define relevant audience segments and preferences for communication channels; using registry data to describe and understand current practice at the level of the center, physician and patients (including equity gaps) to inform design decisions; revising the ICN Model Care Guidelines based on the COMBINE findings to address information needs.

We will engage ICN improvement leaders (clinicians, patients, parents) to co-design and develop resources needed for D&I, including a dissemination campaign that summarizes the evidence and takes advantage of ICN's digital channels and content (e.g., videos, patient and clinician stories, blog posts). We will use the Theoretical Domain Framework [4], to assess specific clinician barriers to adoption and design communication and implementation strategies to address them. We will develop shared decision-making tools under the direction of Dr. Ellen Liptstein, Director of the Program on Shared Decision Making at Cincinnati Children's. The dissemination campaign and shared decision-making tools will be developed with our partner Wondros. We will develop new ICN registry fields and reports to capture data, track medication use changes, and provide clinical decision support (e.g., pre-visit planning reports). We will also develop an implementation "change package" and tools using implementation mapping [5] to support the activities to be undertaken in Aim 2 (see below). These resources will be placed in an accessible, user-friendly digital repository using the existing ICN knowledge-sharing platform (e.g., information sheets, short videos, research papers) for easy reference. Finally, we will develop an evaluation plan that will use ongoing data collection and qualitative data for routine interactions with the community to inform continuous evaluation and optimization of D&I activities.

Expected Outcomes: By the end of the first 9 months of the project, we expect to have community-developed care guidelines, dissemination campaign materials, shared decision-making tools, an implementation plan, resources and a knowledge repository, measures, and reports developed and programmed in the registry, and an evaluation plan to track the impact of dissemination and implementation activities and adapt them over time.

Milestones: We anticipate the following milestones will be achieved during the 9-month design and development phase: 1) updated and ICN-endorsed Model Care Guidelines, 2) Description of current practice pattern variation, stakeholder perspectives and implementation barriers, 3) Dissemination plan and resources, 4) A "change package" of care guidelines, tools to support process change, shared decision-making tools and a digital repository of knowledge, and 5) measures and report specification and programming.

Aim 2: Disseminate broadly across the ICN Network, test and refine a context-specific implementation plan (18 months)

Rationale: Barker's model [6] for scale-up, suggests testing implementation strategies to understand the extent to which they are performing as expected across various contexts (e.g., large center vs. small, private vs. academic) prior to full-scale implementation.

Overall strategy and methods: We will begin by applying the dissemination plan widely across ICN. We will use data on reach and acceptability to refine and adapt communication in real-time. We will use a subgroup of approximately 20 care centers representing different settings and contexts where the dissemination has had success, as initial sites to test and evaluate intervention strategies. Testing innovations in sub-groups of centers is a standard practice in ICN by creating what ICN calls a “Learning Lab.” The implementation mapping process described above, will assist in the final determination of implementation strategies, but we expect they will include: 1) Academic detailing by clinical leaders within the network to help their peers understand the strength of this new evidence and the need to change practice; 2) Transparent measurement and feedback using the ICN registry to track changes in medication use in real-time; 3) Clinical decision support including patient-specific care algorithms to plan and manage the care of patients initiating TNFi medications and population management reports; 4) Collaborative QI, training, and support for practice change including monthly webinars, bi-annual learning sessions, care guidelines, tools and resources to design for segments of ICN centers based on the maturity of their chronic care processes. Collaborative QI also includes practice coaching to help care centers customize new guidelines to each center’s capabilities and contexts; 5) Patient and parents as project co-leaders who will participate in the dissemination campaign and provide peer support for care center family councils.

Evaluation of the pilot test will be guided by the RE-AIM framework [7]. We will monitor dissemination and implementation measures in real-time using the ICN registry and technology platform. Reach will be measured using registry data as the % of patients starting ADA and MTX within 45 days of initiation and the % of patients on IFX not starting MTX within 45 days of initiation; Effectiveness will be measured by modifying the existing monthly registry reports of patient outcomes for those on TNFi therapy with and without MTX - % in clinical remission; % in sustained remission; % in prednisone free remission, % escalating therapy and subsequent addition of immunomodulators within 45 days of TNFi initiation; Adoption will be measured by taking advantage of analytics of ICN’s web-based collaboration hub that is used for care center communication and knowledge management. We will measure the % of care providers viewing/accessing ICN tools (e.g., shared decision-making tools, care planning, and population management tools). We will assess the % of care centers participating in implementation activities (e.g., contributing data monthly, care center teams attending network webinars and bi-annual meetings) and % of clinicians claiming CME and MOC credit for these activities. We will also capture the % of providers who reject the COMBINE recommendations in favor of aggressive drug monitoring or other strategy; Implementation will be measured as the time course of change in adoption metrics (above) using existing statistical process control (SPC) reports from the registry. We will also assess adaptations that individual care centers make to the intervention via routine monthly narrative reports; Maintenance will be tracked using SPC reports on adoption and implementation measures over time. The existing network infrastructure also allows us to capture qualitative data through existing interactions taking place across the network (committee meetings, webinars, conferences, and coaching calls).

Expected Outcomes: By testing the D&I plan in a sub-group of centers, we expect to be able to modify these strategies based on qualitative and quantitative feedback from the community. A central tenet of our approach is the creation of a “learning loop” that gathers feedback from individual physicians who decide **not** to follow the guidelines. Learning from when the COMBINE results are not followed will inform updates to the Model Care Guidelines based on their application in actual practice. We anticipate summarizing the results of our findings at the end of the 18-month pilot testing period to inform the re-design of D&I strategies.

Milestones: Launch of the dissemination campaign and implementation activities, monthly assessment of implementation measures (dose, feasibility, adaptability, fidelity), monthly reports of changes in medication use.

Aim 3: Scale up implementation activities to the entire network (21 months)

Rationale: Scale-up of refined D&I interventions will allow us to reach practices, physicians, and patients across ICN while establishing a feedback learning loop that systematically uses ongoing data to inform ongoing optimization, and the need for new research to advance care.

Overall strategy and methods: During years 3 and 4, we will expand D&I interventions across all care centers in the ICN network, taking advantage of the infrastructure and evaluation capabilities established and tested in years 1 and 2. We will monitor and optimize interventions by leveraging the iterative learning loop established.

Expected Outcomes: Stakeholder champions, including clinicians, parents, and caregivers, together with ICN improvement and analytic experts, will support D&I activities across the network. A process of continuous improvement and optimization of interventions will be underway.

Milestones: Routine monthly reports using the RE-AIM framework. Quarterly reviews of implementation impact. Integration of D&I activities into all network activities. Publication of results.

VI. Budget

Personnel	
<i>Subtotal</i>	\$2,000,000
Travel and Meetings	
<i>Subtotal</i>	\$200,000
Subcontractors	
<i>Subtotal</i>	\$1,000,000
Project Estimate	\$3,200,000

VII. Key Personnel

Kristin Howe, DC, MHA, President and Executive Director of ImproveCareNow will serve as a co-PI of the project and the primary point of contact. She will lead overall program development, coordination of strategic partners and reports to the Helmsley Foundation.

Esther Israel, MD, co-PI of the COMBINE study: Dr. Israel is a pediatric gastroenterologist who leads the ICN site at Mass General Hospital. She will provide clinical expertise and lead the development of academic detailing activities.

Peter Margolis, MD, PhD, Scientific Director ImproveCareNow, Co-Director of the Anderson Center for Health Systems Excellence at Cincinnati Children's Hospital: Dr. Margolis is a pediatrician and epidemiologist who will oversee the design, development and application of improvement and implementation science methods to design the D&I interventions.

Shehzad Saeed, MD, Clinical Director ImproveCareNow: Dr. Saeed is a pediatric gastroenterologist actively engaged in research and quality improvement in pediatric Crohn's disease and ulcerative colitis. He was a key stakeholder in the development of the COMBINE study.

Subcontractors

Hive Networks: Hive is ImproveCareNow's strategic partner and registry/technology vendor. Hive will be responsible for programming and maintenance of the newly developed measures in support of COMBINE implementation.

Participating Centers: ImproveCareNow will contract directly with several participating centers for key personnel and staffing time.

Wondros: Wondros is ICN's communication partner. They are a global creative agency dedicated to solving complex communications challenges to build social movements and inspire action.

References:

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4. Atkins, L., Francis, J., Islam, R. et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implementation Sci* 12, 77 (2017). <https://doi.org/10.1186/s13012-017-0605-9>
5. Walker, T.J., Kohl, H.W., Bartholomew, J.B. et al. Using Implementation Mapping to develop and test an implementation strategy for active learning to promote physical activity in children: a feasibility study using a hybrid type 2 design. *Implement Sci Commun* 3, 26 (2022). <https://doi.org/10.1186/s43058-022-00271-9>
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7. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health*. (1999) 89:1322–7. doi: 10.2105/AJPH.89.9.1322OI