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MAJOR ARTICLE

Clinical Development of Therapeutic Agents for Hospitalized Patients With Influenza: Challenges and Innovations

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Background. Since 1999, the US Food and Drug Administration approved neuraminidase and endonuclease inhibitors to treat uncomplicated outpatient influenza but not severe hospitalized influenza. After the 2009 pandemic, several influenza hospital-based clinical therapeutic trials were unsuccessful, possibly due to certain study factors. Therefore, in 2014, the US Health and Human Services agencies formed a Working Group (WG) to address related clinical challenges.

Methods. Starting in 2014, the WG obtained retrospective data from failed hospital-based influenza therapeutic trials and nontherapeutic hospital-based influenza studies. These data allowed the WG to identify factors that might improve hospital-based therapeutic trials. These included primary clinical endpoints, increased clinical site enrollment, and appropriate baseline enrollment criteria.

Results. During 2018, the WG received retrospective data from a National Institutes of Health hospital-based influenza therapeutic trial that demonstrated time to resolution of respiratory status, which was not a satisfactory primary endpoint. The WG statisticians examined these data and believed that ordinal outcomes might be a more powerful primary endpoint. Johns Hopkins' researchers provided WG data from an emergency-department (ED) triage study to identify patients with confirmed influenza using molecular testing. During the 2013–2014 influenza season, 4 EDs identified 1074 influenza-patients, which suggested that triage testing should increase enrollment by hospital-based clinical trial sites. In 2017, the WG received data from Northwestern Memorial Hospital researchers regarding 703 influenza inpatients over 5 seasons. The WG applied National Early Warning Score (NEWS) at patient baseline to identify appropriate criteria to enroll patients into hospital-based therapeutic trials.

Conclusions. Data received by the WG indicated that hospital-based influenza therapeutic trials could use ordinal outcome analyses, ED triage to identify influenza patients, and NEWS for enrollment criteria.

Keywords. antivirals; clinical site recruitment; enrollment criteria; influenza; therapeutic trial endpoints.

The World Health Organization estimates that, globally, seasonal influenza causes 3 000 000 to 5 000 000 severe illnesses and 290 000 to 650 000 respiratory deaths yearly [1]. The US Centers for Disease Control and Prevention (CDC) estimates that seasonal influenza outbreaks cause 140 000 to 960 000 hospitalizations and 12 000 to 79 000 deaths [2]. Currently, 2 types of antivirals received US Food and Drug Administration (FDA) approval to treat uncomplicated, outpatient influenza in adults and children. These antivirals include neuraminidase inhibitors (NAIs) and, more recently, an endonuclease inhibitor, baloxavir [3, 4]. However, the FDA has not given direct approval to use NAIs to treat more severe disease [5]. Neuraminidase inhibitors are recommended to be used off-label by the CDC and Infectious Diseases Society of America for treatment of influenza in other groups [6, 7]. Off-label use of NAIs for patients with suspected or confirmed influenza includes patients who have pre-existing high-risk medical conditions, progressive disease, or require hospitalization [8]. Currently, baloxavir is approved for early treatment of uncomplicated influenza in persons aged 12 years and older, but it is not recommended by the CDC for use in pregnant women, lactating mothers, those with severe disease, or hospitalized patients, due to lack of data [9].

If widespread resistance emerges for both NAIs and baloxavir, clinicians will have no effective antiviral treatments for influenza, thus development of additional novel effective antivirals are needed [10]. To address resistance possibilities, randomized controlled trials for hospitalized patients with

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influenza are ongoing or completed using monoclonal or polyclonal antibodies, high-titer immune plasma, small-molecule inhibitors, and immune modulatory agents [11–17].

The FDA guidelines exist for evaluation of new antivirals for influenza using hospital-based trial designs. Given no current approval of influenza antivirals for hospitalized patients, noninferiority trials are not feasible because appropriate noninferiority margins do not exist [5]. Currently, the FDA recommends that hospital-based clinical trials be based on a superiority objective, which require large numbers of enrolled subjects and often need multiple seasons to complete. The FDA also acknowledges that investigators have ethical concerns about randomizing hospitalized patients with influenza to placebo or to a new antiviral drug.

The FDA industry guidance for developing hospital-based influenza therapeutic trial design alternatives does exist. Alternatives include (1) a randomized, blinded, dose-response or duration-response trial, whereby a significant dose response is shown or (2) a superiority "add-on" trial, whereby a combination of the investigational therapeutic plus a standard-of-care (SOC) drug (currently NAIs) is superior to placebo and SOC alone [5]. Despite these alternatives, hospital-based trial investigators have expressed concern about the ability to detect clinical benefit of an investigational antiviral given in combination with a NAI, versus NAI alone. These issues present a formable challenge and, so far, no antiviral has received FDA approval for inpatient use.

METHODS

Establishment of Clinical Endpoints Interagency Working Group

The 2009 A/H1N1 pandemic raised concerns by agencies of US Health and Human Services (HHS) of not having FDA-approved influenza antivirals for hospitalized patients. After the pandemic, the Biomedical Advanced Research and Development Authority (BARDA), a division of the Assistant Secretary of Preparedness and Response (ASPR), funded BioCryst to begin a hospital-based trial to assess superiority of peramivir, an intravenous (IV) NAI. Study arms consisted of IV peramivir plus SOC, which consisted of either no NAI or another oral NAI (mostly oseltamivir), compared with placebo plus SOC. In 2012, BioCryst terminated their trial early based upon lack of efficacy in a planned interim analysis of the primary endpoint of "time to clinical resolution" [18].

Because of the 2009 influenza pandemic and the futility of BioCryst's IV peramivir trial, a Working Group (WG) was initiated in April 2014 by US HHS agencies that included the FDA, CDC, ASPR (BARDA), and National Institutes of Health (NIH). Since 2014, Dr. John Tegeris (BARDA) organized monthly WG teleconferences as well as 1 to 2 annual face-to-face meetings to examine available hospital-based influenza therapeutic trial data as well as general inpatient influenza illnesses data. The goal of these WG meetings is to use these data to understand obstacles to conduct influenza therapeutic hospital-based clinical trials. Subsequently, experts from academic institutions and pharmaceutical companies became part of the WG on an ad hoc basis. Currently, 40 experts have become part of the WG, with 27 experts from aforementioned HHS agencies, 10 scientists from academic centers, and 3 researches from pharmaceutical companies (see initial manuscript authors' list and end of manuscript acknowledgements).

RESULTS

So Far, the Working Group Identified Three Obstacles to Hospital-Based Influenza Therapeutic Trials

The major obstacle identified by the WG, triggered by the hospital-based IV peramivir trial, was lack of meaningful, validated trial primary endpoints that demonstrate clinical benefit. By 2017, the WG identified 2 additional important obstacles, triggered from results of pharmaceutical and academic hospital-based influenza therapeutic trials that included low or no trial enrollment at individual clinical sites over multiple influenza seasons, and enrollment criteria that could exclude large numbers of potential subjects. Once these 3 obstacles were recognized, the WG began investigating factors that might overcome these obstacles. This WG article discusses 3 clinical trial factors that may help mitigate these obstacles. Meanwhile, the WG plans to continue exploring issues to improve hospital-based influenza therapeutic trials.

Factor 1: Developing Better Primary Study Endpoints

Presently, key elements to the design of hospital-based influenza therapeutic trials are primary clinical efficacy endpoints, but these endpoints have been challenging to researchers. Table 1 provides information on primary endpoints of 3 hospital-based influenza therapeutic trials. Two trials were fully completed and included GlaxoSmithKline's zanamivir study, which required time-to-clinical response [19, 20], and an NIH high-titer plasma trial, which required time to resolution of respiratory status [14]. Neither trial met their clinical primary efficacy endpoint. The third trial by BioCryst terminated early due to endpoint futility, which required time-to-clinical resolution [21]. It is unclear whether data from these 3 trials indicated need for better therapeutics or better primary efficacy endpoints.

A potentially better primary endpoint is an ordinal outcome that was first proposed for use in hospital-based influenza therapeutic trials by the University of Minnesota group using a theoretical model published in 2017 [22]. Results from this model suggested that a multiple-category, clinical medical care ordinal outcome increases statistical power when compared with other binary endpoints.

During 2017, the NIH published results of a Phase 2b, open-label, hospital-based trial of high-titer plasma and SOC (oseltamivir) compared with SOC [14]. Table 1 demonstrates

Table 1. Completed Influenza Therapeutic Trials

Sponsor (ClinTrials.Gov identifier)	Study Phase	Total Clinical Sites Initially Chosen	Number (%) of Clinical Sites That Enrolled Subjects {Number of Years and Seasons} {{Mean Number of Subjects per Season per Site}}	Number of Subjects Enrolled {Number With Confirmed Influenza Illness}	Enrollment Criteria	Primary Clinical Endpoint	Investigational Product and Statistical Results
GlaxoSmithKline [20] (NCT01231620)	3	170	97 (53%) {4 years and 7 seasons} {{0.922}}	626 {488}	Age criteria: ≥16 years of age Main clinical criteria: suspected or confirmed influenza, -symptoms within 6 days of enrollment ≥2 or more severity criteria including: hypoxia, or need for O_2 supplementation, or ventilator support, tachypnea, tachycardia, or hypertension	Median time (days) to clinical response[a]	Days to clinical response of influenza-positive population: IV 600 mg of zanamvir N = 162 (5.14 days) compared with 300 mg of zanamivir N = 163 (5.87 days) equals −0.73 days, $P = .73$ IV 300 mg of zanamivir N = 163 (5.87 days) compared with oral oseltamivir N = 163, (5.63 days) equals −0.48 days, $P = .39$
BioCryst [21] (NCT00958776)	3	323	86 (27%) {4 years and 7 seasons} {{0.672}}	405 {338}	Age criteria: adults, adolescents and children (aged 6 to 11 years) Clinical criteria for enrollment: Fever and/or reduced O_2 saturation ≥2 of 3 abnormal vital signs ≥1 respiratory symptom ≥1 constitutional symptom ≥1 illness that the investigator's opinion justifies hospitalization	Median time to clinical resolution[b]	Primary analysis was median hours to clinical resolution of the study group that: Oral 600 mg of peramivir plus SOC not including an NAI N = 78 (42.5 hours, 95% C.I. = 3.4–57.9) compared with placebo plus SOC without NAI, N = 43 (49.5 hours, C.I. = 40.0–61.9) $P = .97$
NIH (NIAID) [15] (NCT01052480)	2b	35	20 (57%) {5 years and 5 seasons} {{0.980}}	98 {87}	Age: 0 to 95 years Clinical criteria for enrollment Subjects admitted to the hospital with confirmed with influenza A or B virus infection with room air O_2 saturation of less than 93% or tachypnea	Time to resolution of respiratory status[c]	Number of subjects that normalized their respiratory status by day 28 was 67% for the plasma plus SOC that contains neuraminidase inhibitor (NAI) subjects normalized group N = 42 compared with 53% for SOC with NAI group N = 45, $P = .069$

Abbreviations: C.I., confidence interval; IV, intravenous; NAI, neuraminidase inhibitor; NIAID, National Institute of Allergy and Infectious Diseases; NIH, National Institutes of Health; SOC, standard of care.

[a]Resolution criteria includes the following: (1) both fever resolves and O_2 saturation is ≥95% and (2) two of the following 3 factors: (1) respiratory status resolves or (2) heart rate is ≤100 beats per minute or (3) systolic blood pressure is ≥90 mmHg or hospital discharge

[b]Median time from initiation of study treatment until the following: (1) resolution of ≥4 of 5 vital signs for 24 hours including temperature, O_2 saturation, respiratory rate, heart rate, and systolic blood pressure.

[c]Time to resolution of respiratory status defined as follows: (1) respiratory rate ≤20 breaths per minute for adults or age-defined thresholds of 20 to 38 breaths per minute for children, and a room air O_2 saturation of 93% or more.

that the primary outcome for this NIH trial was time to resolution of respiratory status, which did not quite reach statistical improvement by the high-titer plasma arm. A WG statistician utilized retrospective data from this NIH trial to evaluate a 5-category ordinal outcome consisting of death, intensive care unit (ICU) admission with intubated mechanical ventilation, ICU admission without mechanical ventilation, hospital ward with or without oxygen supplementation, and hospital discharge with or without full function. Ordinal outcomes were examined on treatment days 4, 7, 10, and 14. Figure 1 shows increased progression towards less critical medical care support for the treatment arm that received high-titer plasma plus SOC (NAI) compared with SOC alone for a 5-category ordinal outcome. Figure 1 footnote shows that the common odds ratios were higher for the high-titer plasma plus SOC group compared with SOC alone. The common odds ratio was highest (2.780) for the high-titer plasma plus SOC on Day 7 for the 5-category ordinal outcome. This means that subjects in the plasma plus SOC group were 2.78 times more likely than the SOC alone group to progress to less severe ordinal outcome factors. This retrospective data indicates that ordinal outcome may be a statistically more powerful and useful endpoint for hospital-based influenza therapeutic trials. However, the ordinal outcome endpoint requires prospective evaluation in future blinded inpatient influenza clinical trials.

Table 2 presents primary endpoint use information on 4 ongoing hospital-based influenza therapeutic trials for new investigational products. Three trials are using an ordinal outcome as the primary endpoint [11, 16, 23]. Two of these 3 trials are being conducted by NIH and are using a 6-category ordinal outcome that includes the following: death, ICU admission, hospital ward requiring oxygen supplementation, hospital ward not requiring oxygen, not-hospitalized but not resumed normal function, and not hospitalized and resumed normal function [11, 23]. The third trial, conducted by Janssen, uses a 6-category ordinal outcome that includes the following: death, ICU admission with mechanical ventilation, ICU admission without mechanical ventilation, hospital ward but requiring supplemental oxygen, hospital ward not requiring oxygen supplementation, and not hospitalized (either nonfull or full function) [16]. When completed, data from these 3 trials should help inform a primary ordinal outcome design for future influenza therapeutic clinical trials.

A concern of ordinal outcome categories, such as discharge from ICU or hospital, use of oxygen supplementation, or assessment of function once discharged from the hospital, are more subjective and might be influenced by country, individual hospital medical practices, bed availability, or social factors [24]. However, if these ordinal outcomes are utilized, trial sponsors should provide clear definitions and specific clinical criteria to clinical site researchers in effort to establish consistency in how the study population outcomes are defined and assessed. In addition, ideal time points to assess the ordinal outcome (eg, Day 4 versus Day 7) after initiation of antiviral agents may be dependent on several characteristics. For example, the Janssen [16] clinical trial will assess the ordinal outcome on Day 6 of treatments because their proposed treatment duration is 5 days. Finally, examination of blinded interim data once prespecified proportions (eg, 30% or 50%) of subjects were discharged from the hospital might aid in identifying ideal time points to analyze the ordinal outcome.

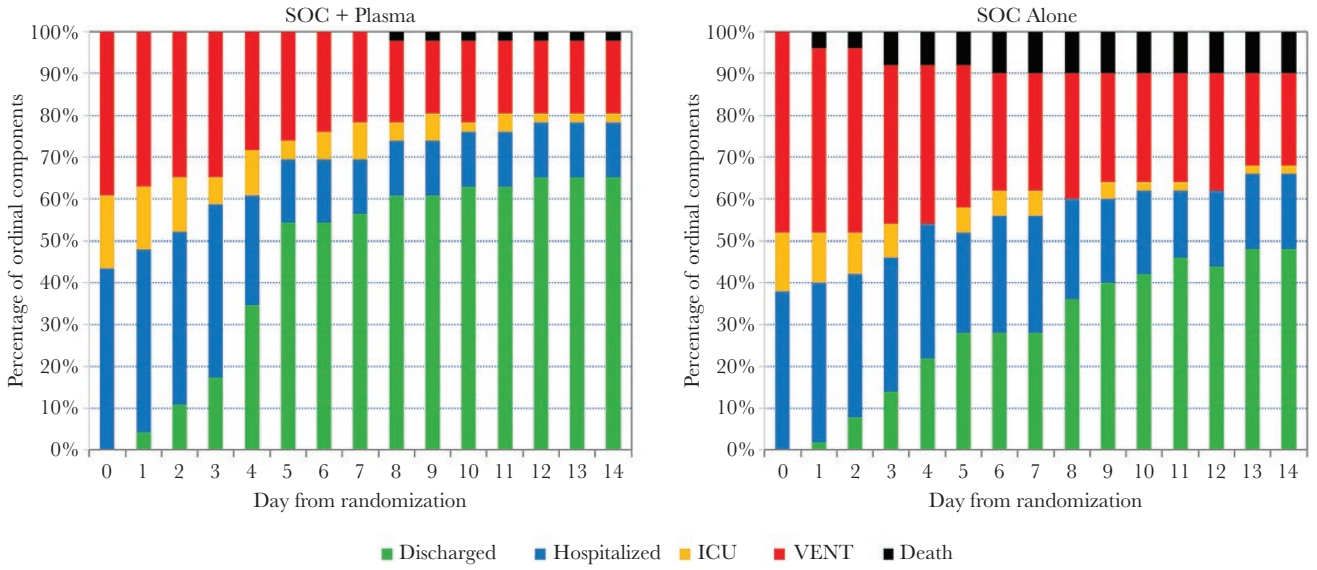

Figure 1. Five-scale ordinal outcomes for high-titer plasma plus standard of care (SOC) or SOC alone. Standard of care in this case was oseltamivir. Note the common odds ratio (OR) and 95% confidence interval (C.I.) and *P* value were estimated based upon an ordinal outcome logistic regression model, and the *P* values were based on likelihood ratio test from the ordinal logistic regression model. Results: Day 4 (OR = 1.9; 95% C.I., 0.9–4.0; *P* = .086); Day 7 (OR = 2.8; 95% C.I., 1.3–5.9, *P* = .008); Day 10 (OR = 2.3; 95% C.I., 1.1–5.0; *P* = .035); Day 14 (OR = 2.1; 95% C.I., 0.9–4.5; *P* = .071).

Table 2. Ongoing Hospital-Based Influenza Therapeutic Trials

Sponsor (ClinTrials.gov code) {Study Phase}	Investigational Products and Proposed Study Arms	Enrollment Criteria	Number Subjects	Number Clinical Sites	Primary Clinical Endpoint and primary Analyses
Visterra [13] (NCT03040141) {Phase 2b}	1. One low-dose IV Mab (2000 mg) and SOC[a] 2. One high-dose IV Mab (4000 mg) + SOC 3. One IV dose placebo + SOC	Age 18 years or older Clinical inclusion criteria: Confirmed influenza A illness Requires O_2 support including any positive pressure ventilation	390	TBD	Time to cessation of oxygen support resulting in a stable SpO_2 greater than 92% on room air
NIH (NIAID) [23] (NCT02572817) {Phase 3}	1. One IV dose of high-titer plasma 250–350 mL per unit or pediatric equivalent with both an influenza A/H1N1 or A/H3N2 titer ≥1:80 2. One IV dose of low-titer plasma 250–350 mL per unit or pediatric equivalent with both an influenza A/H1N1 or A/H3N2 titer ≤1:10	1. Age children ≥2 weeks, adult and seniors Clinical inclusion criteria: 2. Hospitalized for influenza with anticipated hospitalization >24 hours after randomization 3. NEWS[b] score ≥3 for adults or 4. Pediatric early warning score ≥3 within 12 hours before randomization	300	41	Six-point, proportional ordinal outcome[c] at day 7
NIH (NIAID) [11] (NCT02287467) {Phase 3}	1. Hyperimmune IVIG 0.25 g/kg (maximum 24.75 g) + SOC 2. Placebo IV plus SOC	1. Age 18 years and older Clinical inclusion criteria: 2. Influenza anticipated hospitalization >24 hours 3. NEWS[b] score ≥2 at screening	320	21	Six-point, proportional ordinal outcome[c] at day 7
Janssen [16] (NCT03376321) {Phase 3}	1. Oral pimodivir (small molecule) 600 mg twice a day for 5 days 2. SOC treatment determined by the site investigator based on local practice. This SOC may or may not include a neuraminidase inhibitor	1. Age 13 to 85 years Clinical inclusion criteria: 2. Requires hospitalization 3. Enrollment ≤96 hours after onset of influenza symptoms 4. O_2 saturation < 94% on room air or with known O_2 saturation <94% must have O_2 saturation decline of ≥3% 5. NEWS[b] of ≥4	600	TBD	Six-point hospital recovery scale (ordinal outcome[d]) at day 6

Abbreviations: ICU, intensive care unit; IV, intravenous; IVIG, IV immunoglobulin; Mab, monoclonal antibody; NEWS, National Early Warning Score; SOC, standard of care; TBD, to be determined.

[a]SOC includes 75 mg of oseltamivir twice a day for 5 days.

[b]NEWS developed in England [30].

[c]Six-point scale contains percentage of participants for each factor from most severe to least severe on day 7 after start of therapy: (1) death, (2) ICU admission, (3) non-ICU requiring O_2 supplementation, (4) non-ICU not requiring O_2 supplementation, (5) not hospitalized but not resumed normal function, (6) not hospitalized and resumed normal function.

[d]Six-point ordinal scale (hospital recovery scale) contains percentage of participants for each factor from most to least severe on day 6 after start of therapy: (1) death, (2) admitted to the ICU requiring invasive mechanical ventilation, (3) admitted to the ICU not requiring invasive mechanical ventilation, (4) non-ICU admission requiring supplemental oxygen, (5) non-ICU admission not requiring oxygen supplementation, and (6) not hospitalized.

The FDA notes other possible primary clinical endpoints to evaluate hospital-based therapeutic trials. For example, time to events, such as total time in the ICU or hospital, or time to normalization of vital signs and symptoms [5]. In addition, of time-to-cessation of oxygen support and restoration of normal or baseline oxygen saturation would seem appropriate endpoint because many patients with confirmed influenza hospitalized with some degree of respiratory distress [25]. In summary, the WG will continue assessments of present and future endpoints in hopes of developing more effective, novel therapeutics for severe influenza.

To summarize Factor 1, our WG believes that hospital-based influenza therapeutic trials must have effective primary study endpoints. The ordinal outcome could be a valuable endpoint if enrolled subjects have relatively severe illnesses, but it will be important to identify methods for clinical site researchers to unify ordinal outcomes to have objective measures. However, current Phase 3 hospital-based therapeutic studies have not yet finished, and, even when they do, investigators need to assess ideal items to include in the ordinal outcome. Currently, using post hoc versus preplanned data is a study limitation of variance and statistical power for various ordinal outcome designs.

Factor 2: Improving Enrollment Into Therapeutic Trials

Prior hospital-based influenza therapeutic trials suffered from very slow enrollment. Table 1 demonstrates 3 completed hospital-based influenza therapeutic trials that took 4 to 5 years

to finish subject enrollment over 5 to 7 influenza seasons in the Northern and Southern Hemispheres [14, 20, 21]. Average enrollment into these 3 trials were 0.67 to 0.98 subjects randomized per clinical site per influenza season, and 47% to 73% of the clinical sites failed to enroll any subjects. Low site enrollment likely has a negative impact on trial randomization balance by site because clinical hospital management and supportive care of hospitalized influenza patients vary from hospital to hospital within and among countries.

A potential strategy to achieve higher site enrollment each influenza season for hospital-based trials focuses on early identification of confirmed influenza by emergency departments (EDs). Emergency departments are often the location of initial patient contact for respiratory illness. Investigators from Johns Hopkins Hospital (JHH) ED in Baltimore, along with investigators from 3 other ED Influenza Consortium Hospitals (see Acknowledgments), derived a routine triage screening protocol to more rapidly identify influenza patients early during their visit [26]. During the 2013–2014 season, these 4 hospitals had their ED triage staff use a clinical decision guideline (CDG), created by the Influenza Consortium Hospitals, to evaluate adults who presented to the ED with acute respiratory illness for influenza testing. Per the CDG, triage staff evaluated patients for the presence of cough (2 points), subjective fever symptoms (1 point), headache (1 point), and triage temperature of >100.4°F (1 point). If the CDG was positive, defined as score greater than 2, triage staff obtained the patient's verbal consent to obtain a nasopharyngeal (NP) swab. The NP sample went to the hospital laboratory for qualitative reverse-transcription polymerase chain reaction (RT-PCR) testing (Xpert Flu) for influenza A and B. Emergency department clinicians received RT-PCR results from the laboratory at a median time of 166 minutes after obtaining the NP sample. In one influenza season, 1074 (18%) of 5937 patient NP tests were positive for influenza across the 4 ED sites (range, 178 to 367 positive tests per site). Note that 185 (17.2%) of those 1074 patients were hospitalized during their ED visit. This triage approach represents a promising model for early identification of large numbers of ED patients with confirmed influenza. This CDG method should improve enrollment into future hospital-based influenza therapeutic trials. In addition, triage testing could benefit ED patients in terms of more rapid medical treatment and better infection control.

In a follow-on investigation, JHH and Maricopa Medical Center (MMC) researchers conducted an open-label, pilot influenza therapeutic trial to demonstrate the utility of ED triage influenza testing to enroll patients into a hospital-based therapeutic trial. The FDA approved this Investigational New Drug (IND) inpatient clinical treatment trial that lasted for the 2015–2016 and 2016–2017 influenza seasons [27]. To be eligible for this trial, patients had to be 18 years of age or older with RT-PCR-confirmed influenza, who met CDC criteria for NAI treatment, which includes hospitalization, as well as severe, complicated, or progressive disease [6]. Meanwhile, the patient's ED clinician independently decided whether the subject was to be hospitalized or discharged from the ED. Eligible patients that consented to be in this inpatient trial were enrolled and randomized to receive either oral oseltamivir twice daily for 5 days or a single dose of IV peramivir during their hospitalization. Table 3 demonstrates that triage RT-PCR testing for influenza was associated with robust enrollment (n = 61) into this inpatient pilot trial over 2 influenza seasons. During the 2015–2016 influenza season, JHH triage identified 274 patients with positive influenza RT-PCR tests with 94 patients hospitalized and 20 (21%) of the patients enrolled into the trial. During the 2016–2017 season, JHH and MMC enrolled 41 hospitalized subjects (overall numbers of patients hospitalized not available). Compared to low per-site enrollment numbers in previous hospital-based influenza therapeutic trials, these study results are encouraging. However, we also recognize this JHH study's use of 2 FDA-approved outpatient influenza antivirals makes direct comparisons of this trial to enrollment into Phase 3 registrational hospital-based novel therapeutic trials difficult. So far, the WG is not aware of active studies that uniformly use ED triage influenza testing for hospital-based influenza trials.

To summarize Factor 2, assessing ED triage protocols in future, hospital-based, influenza therapeutic trials could confirm whether this JHH methodology is reproducible, cost effective, and results in robust enrollment. Increased site enrollment should improve future trial results, quality of randomization, and reduce costs. Emergency department triage could also reduce the number of influenza seasons to complete the trial, thereby reducing influenza interseasonal variability. Finally, rapid point-of-care multiplex molecular diagnostics are being deployed across EDs nationwide and are now FDA-approved and Clinical Laboratory Improvement Amendment-waved assays that produce results within 15 to 30 minutes [28, 29]. In addition, rapid molecular testing, if applied early at a clinical

Table 3. Number of Subjects Enrolled Into Influenza Therapeutic[a] Study Using Emergency Department Clinical Decision Guideline Triage Protocol[b]

Influenza Season	Total Enrollment	Johns Hopkins Hospital	Maricopa Medical Center
2015–2016[c,d]	20	20	Not done
2016–2017	41	33	8
Both seasons	61	53	8

Abbreviations: FDA, US Food and Drug Administration; JHH, Johns Hopkins Hospital; RT-PCR, reverse transcription-polymerase chain reaction.

[a]Pilot, FDA-approved Investigational New Drug study to test enrollment using oral oseltamivir or intravenous peramivir for inpatients and outpatients [27].

[b]Clinical Decision Guideline [26].

[c]During the 2015–2016 season, 1674 nasal samples were obtained for testing, 274 (16%) of which had positive RT-PCR tests, and 94 (34%) patients with positive tests were admitted regardless of enrollment to the pilot study. Of the 94 JHH patients admitted, 20 (21%) were enrolled into the hospitalized study.

[d]Of the 94 admissions, 26 (28%) were discharged within 2 days.

study site, such as outpatient facility or ED, should help increase enrollment for outpatient influenza therapeutic studies. However, there are other factors involved that affect enrollment that include clinical site enrollment, research resources, as well as motivated and trained investigators and clinical coordinators that should be addressed in future studies.

Factor 3: Optimized Baseline Inclusion Criteria for Hospital-Based Therapeutic Trials

Patients hospitalized with confirmed influenza can have illnesses of differing severity, thus leading to challenges for therapeutic trials to identify and enroll ideal subjects with relatively severe infection. However, overly restrictive criteria may substantially reduce site enrollment. Table 4 shows retrospective data from 3 trials that were examined by the WG to identify potentially overly restrictive criteria that limited site enrollment. For example, these 3 completed hospital-based trials had 1 or more clinical enrollment requirements including oxygen supplementation or hypoxia, abnormal vital signs, ventilator support, or start of influenza symptoms within 6 days. As a result, these trials had very low site enrollment each influenza season and took 4 or 5 years to complete as previously discussed in the Factor 2 discussion [14, 20, 21].

The WG sought information for more optimized inclusion criteria. In 2012, British investigators developed the National Early Warning Score (NEWS) to assess severity of acute illness [30]. National Early Warning Score utilizes vital signs, oxygen saturation, oxygen supplementation, and level-of-consciousness to provide a total score of illness severity from 0 to 20. As such, clinicians could use NEWS to estimate initial severity of influenza in a heterogeneous population of hospitalized patients and assist in identifying appropriate enrollment criteria into a hospital-based therapeutic trial. Although respiratory illness is common in hospitalized influenza patients, not all cases are severe enough to result in hypoxia, oxygen supplementation, or ICU admission early in the disease course [25]. A potential advantage of NEWS is that it covers not just respiratory disease but other manifestations of influenza, such as encephalopathy, severe myalgia, or organ dysfunctions. Using NEWS for enrollment criteria could potentially result in robust recruitment and potentially capture a broader illness population. More importantly, NEWS main value could potentially identify sufficiently ill study populations to demonstrate a beneficial novel therapeutic treatment effect.

To test this hypothesis, Northwestern Memorial Hospital (NMH) academic researchers provided the WG with deidentified data from 703 hospitalized patients with confirmed influenza over period of 5 years (2009–2014) [31]. This deidentified NMH medical data, which was not a therapeutic trial, allowed estimation of percentages of patients potentially eligible for enrollment into future hospital-based influenza therapeutic trials based upon certain criteria. Table 4 demonstrates several considerations for baseline enrollment criteria using the NMH data. The most restrictive enrollment consideration was baseline admission to the ICU, whereby only 1% of hospitalized patients are recruited. Other Table 4 baseline recruitment considerations consists of time from symptom onset to enrollment by ≤72 or ≤96 hours, clinical need for oxygen supplementation, oxygen saturation <93% on room air, baseline NEWS for acute illness from >2 to >8, combination of NEWS >3 or oxygen

Table 4. Numbers of Northwestern Memorial Hospitalized Patients [31] With Documented Influenza Illness (2009–2014)

Baseline Characteristics	Number (%) of Patients Potentially Eligible for Enrollment to an Influenza Therapeutic Trial	Number (%) of Patients Discharged Within 48 Hours of Admission
All patients	703 (100%)	
ICU on admission	7 of 703 (1%)	0
Time from symptom onset to admission ≤72 hours	315 of 703 (45%)	39 of 315 (12%)
Time from symptom onset to admission ≤96 hours	440 of 703 (63%)	56 of 440 (13%)
O_2 supplementation required	455 of 703 (65%)	76 of 455 (17%)
Oxygen saturation <93%	156 of 699 (22%)	11 of 156 (7%)
O_2 supplementation and O_2 saturation ≤93%	65 of 699 (9%)	8 of 65 (12%)
NEWS[a] >2	493 of 698[b] (71%)	53 of 493 (11%)
NEWS >3	403 of 698 (58%)	39 of 403 (10%)
NEWS >4	294 of 698 (42%)	23 of 294 (8%)
NEWS >5	222 of 698 (32%)	9 of 222 (4%)
NEWS >6	156 of 698 (22%)	2 of 161 (1%)
NEWS >7	102 of 698 (15%)	1 of 102 (1%)
NEWS >8	62 of 698 (9%)	0
NEWS >3 or O_2 supplementation required[c]	677 of 698 (97%)	87 of 677 (13%)
NEWS >3 or oxygen saturation <93%[c]	415 of 698 (61%)	40 of 415 (10%)

Abbreviations: ICU, intensive care unit; NEWS, National Early Warning Score; NMH, Northwestern Memorial Hospital.

[a]See Ref. [30].

[b]Six hundred ninety-eight of the 703 patients had baseline NMH information [31] for NEWS scoring.

[c]Note that the bottom 2 rows contain data on potential eligibility and early discharge if mixed criteria are used for enrollment.

saturation <93%, and lastly baseline NEWS >3 or oxygen supplementation. This last baseline had the highest enrollment possibility of 97%.

Alternatively, some patients have other hospitalization criteria including advanced age or underlying high-risk medical conditions. It would be challenging to demonstrate the clinical benefit of new antiviral agents if hospitalized subjects with mild influenza enrolled into a therapeutic trial and discharged quickly. For example, Table 3 footnote shows that 26 (28%) of 94 JHH patients hospitalized with confirmed influenza during the 2015–2016 season were discharged within 2 days of admission [27]. In addition, an older published study of 333 patients admitted from the ED to 75 US hospitals were evaluated for discharged issues [32]. Discharged data from that study revealed that 37% of these patients had a minor severity level of illness and a mean length of stay of 2.9 days. Finally, Table 4 reveals that 89 (13%) of 698 NMH-confirmed influenza patients admitted from 2009 to 2014 were discharged from the hospital within 24 to 48 hours [31]. If a hospital-based therapeutic trial is targeted to treat severe influenza illness, it is important that enrolled populations have a relatively higher-level of illness.

To summarize Factor 3, optimized inclusion criteria for hospital-based influenza therapeutic trials is important. Four current hospital-based trials are using NEWS as recruitment criteria [11, 13, 16, 23]. In addition, it is important that enrolled populations have a relatively higher level of illness at baseline.

CONCLUSIONS

To summarize this report, our WG identified 3 potentially useful factors that could increase the performance of hospital-based influenza therapeutic trials. These factors include the following: (1) use of ordinal outcome as a primary or key clinical endpoint; (2) an ED triage system using rapid RT-PCR testing to quickly identify influenza patients, thereby increasing site enrollment; and (3) baseline enrollment criteria using NEWS to identify a more diversified group of patients with relatively severe influenza to improve the demonstration of antiviral effectiveness. Finally, some of the factors discussed in this report might be useful for clinical trials of other viral or bacterial respiratory diseases, including emerging pathogens.

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