22nd Cambridge International Manufacturing Symposium – Full Papers and Extended Abstracts
University of Cambridge, 27th – 28th September 2018

Combining field data analysis and simulation to evaluate an alternative Just-In-Time clinical trial supply strategy

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Abstract

This paper combines recurrence analysis of field data from clinical trial supply chain (CTSC) with a proof-of-concept inventory profile simulation to evaluate an alternative packing capability that supports just-in-time (JIT) manufacturing and distribution of investigational medicinal products (IMP). Assumptions for JIT packing supply capabilities and expedite quality release were taken from a detailed design prototype recently commissioned by a leading pharmaceutical consortium. The suggested technological intervention is assessed in its ability to reduce finished good inventory while adequately responding to the dynamics of uncertain patient recruitment and required service levels. The proposed combination of field data analysis and simulation enables practitioners to consider the possibilities for a more economically viable adaptive clinical trial supply based on JIT technologies and near real-time product utilisation information across multiple locations.

Keywords: clinical trials; data analytics; pharmaceutical supply chains; inventory simulation

1. Introduction

Global pharmaceutical companies spent approximatively USD 93.8 bn on Research and Development in 2017, a significant part of which was destined to support lengthy and inherently risky clinical trials (BMI, 2017). With the increasing downward pressure in healthcare spending due to the availability of generic (or multisource) medicines, the commercial viability of innovator brands has largely depended on the ability to invest in more comprehensive clinical trials for Investigational Medicinal Products (IMP), recouped through aggressive marketing and sales (Friedli, 2006). To achieve service levels such that clinical trials are carried out safely, ethically and in compliance with tight regulations across multiple locations globally, availability is often prioritised over efficiency across the Clinical Trial Supply Chain (CTSC), overcompensating stock-out risk with high inventory levels (DHL, 2017). On average, 45% of manufactured IMP gets all the way through packing, shipping, and dispensing to the patient (Lamberti *et al.*, 2016).

The development of automated and autonomous clinical supply capabilities is regarded by the UK industrial digitalisation strategy as key to reduce lead-times and enable more responsive clinical supply (*Made Smarter Review,* 2017). A leading pharmaceutical consortium has recently commissioned a prototype Just-In-Time (JIT) clinical pharmacy concept, providing packing supply and expedite release capabilities, which is now in the detailed design stage.

The aim of this paper is to provide an approach supporting the complex ex-ante assessment required for emerging technologies such as the JIT clinical pharmacy mentioned above. To achieve this aim, retrospective CTSC field data analysis is combined with multi-tier inventory simulation. The research question to be addressed through the proposed approach is as follows: **RQ** - "*To what extent would a JIT clinical pharmacy concept reduce unused inventory and improve service levels across a CTSC?*"

The rationale for the research presented in this paper is that the assessment of specific technological interventions is often left outside the scope of CTSC modelling. Among the few exceptions, is the use of simulation to evaluate 'smart labelling' technologies in clinical supply (Paricio, 2016). More often, research aims at optimising inventory positioning across the CTSC with a focus on distribution networks, without detailing manufacturing and patient-dispensing activities (for example, Fleischhacker *et al.*, 2015). More detailed models complement optimisation with simulation, but are less concerned with extensive analysis of empirical data (for example, Chen *et al.*, 2012); or, when real-world data usage is claimed, their exploration and analysis is not made explicit (for example Abdelkafi *et al.*, 2009). Conversely, purely data-driven approaches employ statistical inference to estimate trade-offs between inventory overage and the risk of a clinical study experiencing shortage, while remaining agnostic to specific CTSC network configurations and manufacturing technologies (for example, Anisimov, 2009).

In the reminder of this paper, the proposed approach is illustrated and applied to a hypothetical, simplified case underpinned by evidence from a completed clinical trial. Findings exemplify possible improvements on inventory and service levels assuming that clinical supply for the examined trial had occurred under conditions compatible with the JIT pharmacy concept.

2. Materials and methods

Supplying to clinical development programs exhibits characteristic operational challenges. Downstream, the demand is determined by the number of clinical centres participating in the study, the patients recruited and their usage profile. Variations in patient recruitment and dispensing patterns across centres can have significant repercussions on the design of supply and inventory strategy for an IMP (Anisimov, 2009). Upstream, an IMP is typically manufactured with methods that are still under development, and with limited evidence on its stability; for release to use, individual batches require quality assurance and must conform to global stewardship requirements, as well as, its nuanced regional variations (Rees, 2011).

Reflecting these general characteristics, a 'current state' scenario was formulated based on data from a completed double-blind, multicentre Phase IIIa clinical trial provided by industry partners. The study involved 1,800+ patients recruited through 160+ clinical centres (henceforth just centres), and randomised to either a test product (IMP), or a comparator product and the corresponding placebos. All products were sourced by the centres from six distribution hubs across Eastern Asia, North America, Russia and Europe. The raw data cover the occurrence of the following events: 1) release of manufacturing jobs; 2) execution of shipment orders to clinics, either directly or via distribution hubs; and 3) dispensing to patients.

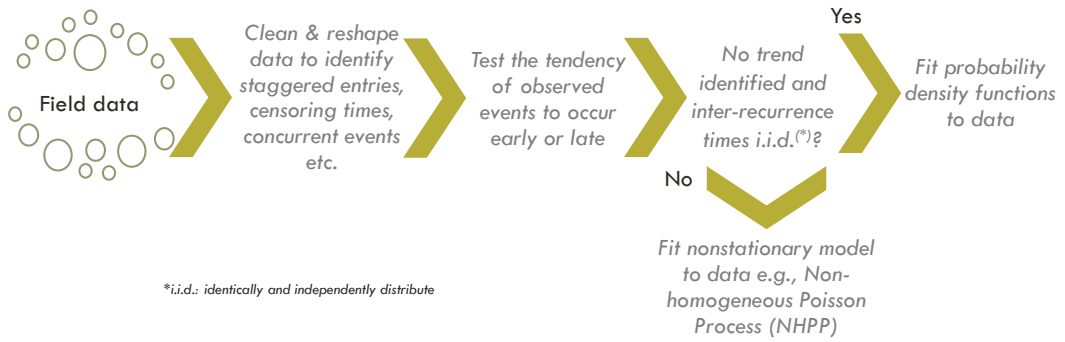

Figure 1. Strategy for the analysis of CTSC field data with a focus on recurrent events

Patient recruitment events were outside the scope of the data provided, and hence only approximated. In the 'future state' scenario, a hypothetical 'make-to-order' manufacturing setting is introduced, reflecting assumptions regarding the operational capabilities of a JIT clinical pharmacy concept taken from expert judgment and detailed prototype design.

In the absence of specific guidance on the retrospective analysis of CTSC data, an existing strategy proposed by Settanni *et al.* (2016) and originally meant for repairable airborne items has been adapted as shown in Figure 1. The strategy emphasises recurrence data, which are the empirical basis for modelling patterns in the occurrence of specific events as stochastic point processes. This strategy was applied to the raw data to analyse two types of recurrent events in a CTSC context: 1) arrival of shipment orders at distribution hubs, linked to individual manufacturing jobs; and 2) patients visit at clinics, and dispensing of the product they are randomised to. Insights obtained from the retrospective analysis of filed data were then used to simulate a range of performance levels for both 'current' and 'future' state CTSC scenarios, in terms of unused inventory and service level to the patient. Similarly to field data analysis, there is no widely-adopted approach to simulation in the specific context considered here. In general, the simulation of JIT manufacturing systems has received attention since the 1980s (for example Fallon and Browne, 1988). However, the application of JIT to pharmaceutical supply chains is still relatively under-researched, and largely associated with the concept of 'operational excellence' in business practice (for example, Friedli, 2006). Strohhecker *et al.* (2013) provide one of the few applications of simulation within a pharmaceutical manufacturing site to investigate the viability of a decentralised, leaner, and demand-pull operations scenario.

Discrete event simulation (DES) was deemed suitable to experiment with a new design that could create non-obvious interactions between a manufacturing system's elements, with a focus on the occurrence of key, state-changing point events in time (Banks, 2010). To facilitate the engagement of industry partners, the simulation model was built and run using widely adopted, commercial-off-the-shelf software WITNESS [Lanner Group, UK]. A review of alternative tools for supply chain simulation is beyond the scope of this paper and can be found elsewhere (Terzi and Cavalieri, 2004).

Table 1. Manufacturing jobs data layout for recurrence time analysis

q	**Start time** S_q	**Stop time** T_q	$\ln S_q$	$\ln T_q$	$S_q^{\hat{\beta}}$	$T_q^{\hat{\beta}}$	$T_q^{\hat{\beta}} - S_q^{\hat{\beta}}$	$T_q^{\hat{\beta}} \ln T_q - S_q^{\hat{\beta}} \ln S_q$	N_q
1	-	222.726	-	5.406	-	430.712	430.712	2,328.404	18
2	0.009	374.726	-4.722	5.926	0.005	772.135	772.130	4,575.845	2
3	12.411	374.726	2.519	5.926	16.875	772.135	755.260	4,533.321	13
4	20.384	374.726	3.015	5.926	29.445	772.135	742.690	4,487.054	18
5	266.241	619.726	5.584	6.429	526.193	1,357.790	831.598	5,791.141	2
							3,532.389	21,715.765	53

Notes. q: patient id; N_q: events per patient in Table 2; $\hat{\beta}$ is computed as described in the main text.

3. Findings

To keep the analysis concise and transparent, this section illustrates findings for a streamlined version of the CTSC investigated, employing a downsized excerpt from the original dataset. The subset consists of orders shipping events and patient dispensing events for two centres only, and is limited to the IMP (comparator and placebos are excluded from the example).

3.1. Findings from field data analysis

Large part of the field data considered here is a track record of recurrence time, such as the times at which patients are dispensed the IMP, or at which kits from specific manufacturing jobs are shipped. These can be regarded as point events from a random process. It is good practice to test whether a sequence of times to consecutive events exhibits a trend: in the presence of a trend it is legitimate to assume that the rate at which events occur is non-stationary over time as, for example, in a nonhomogeneous Poisson process - NHPP (Ascher, 1983).

To illustrate this point, Figure 2 summarises the relevant empirical data (bottom half) and their statistical approximation (top half). Using an example subset of order shipping events, Table 1 and 2 organise recurrence time data for the underpinning numerical analysis as follows:

- Data are obtained from k items – e.g. manufacturing jobs or patients. Each item q $(q = 1, \dots, k)$ is observed from S_q to T_q – e.g., from regulatory release to the time of expiry suggested by the stability studies on the IMP; or from patient enrolment until the study terminates, or the patient drops out. Separate analysis of S_q data in the case of patient enrolment is advisable (e.g. Anisimov and Fedorov, 2007). Due to restrictions on data-sharing, the enrolment times used in this example are crude approximations.

- A generic item experiences a total of N_q events, and each event i $\left(i = 1, \dots, N_q\right)$ occurs after a certain amount of time-on-study X_{iq} has elapsed. The time-on-study is measured on a common timeline originating at the earliest item entry time. Table 2 also reports the time-on-study for each item at each event, taking into account the item's staggered entry. Inter-arrival times are times between two consecutive events for a given item.

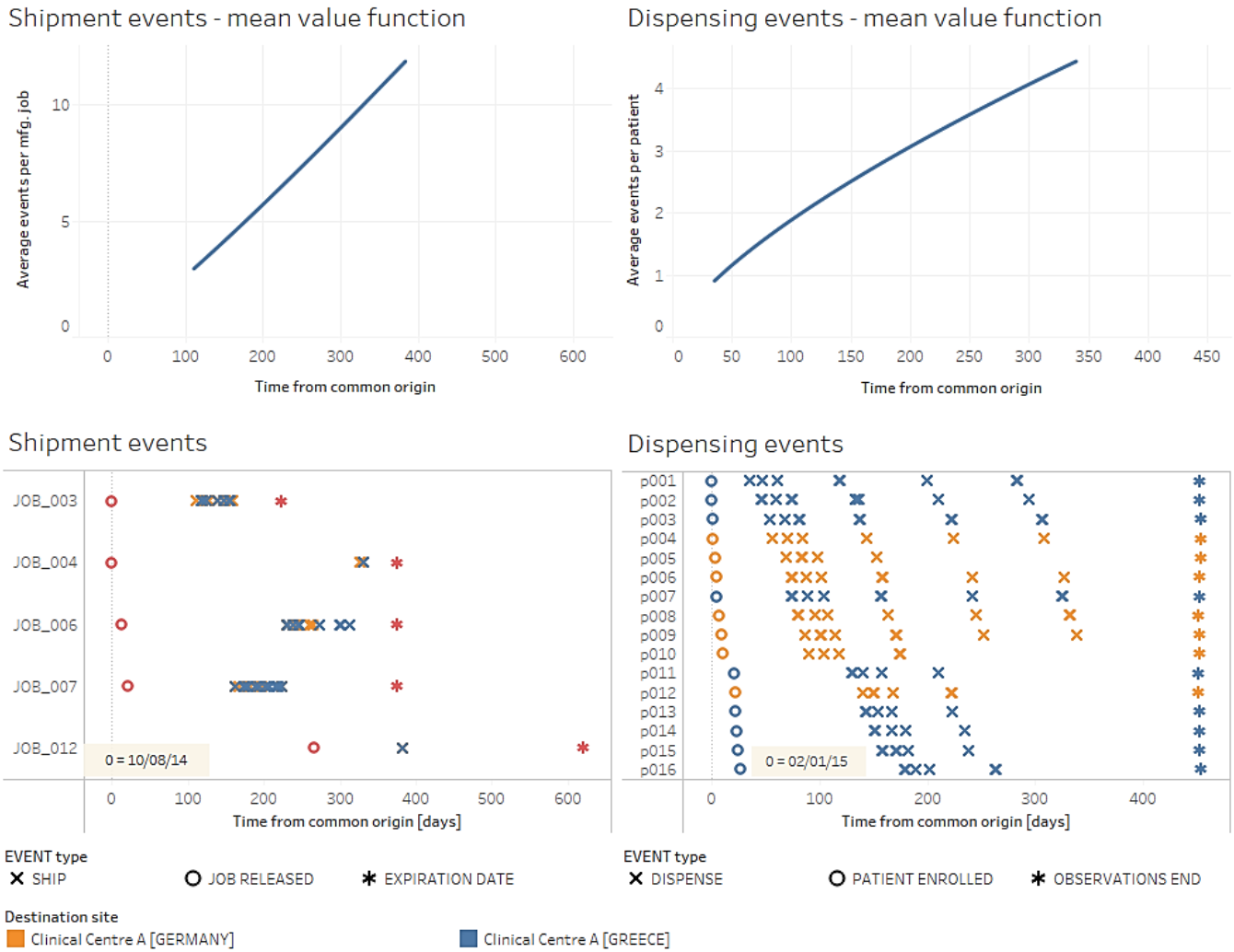

Figure 2. Recurrence time analysis of field data on shipment and patient dispensing events. Mean value functions computed as described in main text.

Table 2. Order shipping events linked to manufacturing jobs – layout for recurrence time analysis

i	**q**	**TOS** X_{iq}	$\ln X_{iq}$	**MVF** $\hat{\lambda} X_{iq}^{\hat{\beta}}$	**T**	**IAT**	**Item's time-on-study at event**					**Cumul. age** x_i
							1	**2**	**3**	**4**	**5**	
1	1	110.85	4.70	2.95	S	110.85	***110.85***	110.84	98.44	90.47	-	410.59
2	1	117.73	4.76	3.16	S	6.88	***117.73***	117.72	105.32	97.34	-	438.10
3	1	118.73	4.77	3.19	S	1.00	***118.73***	118.72	106.32	98.34	-	442.10
4	1	119.43	4.78	3.21	S	16.80	***119.43***	119.42	107.02	99.04	-	444.90
5	1	124.73	4.82	3.37	S	5.30	***124.73***	124.72	112.32	104.34	-	466.10
6	1	125.48	4.83	3.39	S	17.97	***125.48***	125.47	113.06	105.09	-	469.10
7	1	127.85	4.85	3.46	S	2.37	***127.85***	127.84	115.44	107.46	-	478.59
8	1	138.95	4.93	3.80	S	11.10	***138.95***	138.94	126.54	118.56	-	522.99
9	1	139.14	4.93	3.81	S	4.50	***139.14***	139.13	126.72	118.75	-	523.74
10	1	139.81	4.94	3.83	S	16.14	***139.81***	139.80	127.40	119.42	-	526.43
11	1	146.93	4.99	4.05	S	7.12	***146.93***	146.92	134.52	126.55	-	554.91
12	1	147.66	4.99	4.07	S	17.58	***147.66***	147.65	135.25	127.28	-	557.84
13	1	149.05	5.00	4.11	S	1.39	***149.05***	149.05	136.64	128.67	-	563.42
14	1	149.29	5.00	4.12	S	5.76	***149.29***	149.29	136.88	128.91	-	564.38
15	1	153.74	5.03	4.26	S	4.45	***153.74***	153.74	141.33	133.36	-	582.17
16	1	154.01	5.03	4.27	S	6.26	***154.01***	154.00	141.59	133.62	-	583.22
17	1	155.88	5.04	4.33	S	1.87	***155.88***	155.87	143.47	135.50	-	590.71
18	1	159.49	5.07	4.44	S	3.61	***159.49***	159.48	147.07	139.10	-	605.14
19	4	161.84	5.08	4.51	S	141.46	161.84	161.83	149.43	***141.46***	-	614.57
20	4	162.08	5.08	4.52	S	5.59	162.08	162.07	149.66	***141.69***	-	615.50
21	4	167.39	5.12	4.69	S	5.32	167.39	167.38	154.98	***147.01***	-	636.76
22	4	173.76	5.15	4.89	S	6.37	173.76	173.75	161.35	***153.37***	-	662.23
23	4	174.42	5.16	4.91	S	15.94	174.42	174.41	162.01	***154.04***	-	664.89
24	4	175.12	5.16	4.93	S	16.63	175.12	175.11	162.70	***154.73***	-	667.66
25	4	180.21	5.19	5.09	S	5.10	180.21	180.21	167.80	***159.83***	-	688.06
26	4	182.43	5.20	5.16	S	2.22	182.43	182.42	170.02	***162.05***	-	696.93
27	4	190.62	5.25	5.42	S	8.19	190.62	190.62	178.21	***170.24***	-	729.70
28	4	194.16	5.26	5.54	S	3.54	194.16	194.16	181.75	***173.78***	-	743.85
29	4	194.21	5.26	5.54	S	1.07	194.21	194.20	181.80	***173.83***	-	744.03
30	4	197.39	5.28	5.64	S	3.18	197.39	197.38	184.98	***177.00***	-	756.74
31	4	202.48	5.31	5.80	S	5.09	202.48	202.47	190.07	***182.09***	-	777.11
32	4	207.75	5.33	5.97	S	5.27	207.75	207.74	195.33	***187.36***	-	798.18
33	4	216.36	5.37	6.25	S	8.62	216.36	216.35	203.95	***195.98***	-	832.65
34	4	219.43	5.39	6.35	S	3.07	219.43	219.42	207.02	***199.05***	-	844.93
-	1	{222.73}	-	-	EO	{63.24}	***222.73***	222.72	210.32	202.34	-	{858.10}
35	4	224.00	5.41	6.50	S	4.56	-	223.99	211.59	***203.61***	-	639.19
36	4	224.42	5.41	6.51	S	10.08	-	224.41	212.01	***204.03***	-	640.45
37	3	230.80	5.44	6.72	S	218.39	-	230.79	***218.39***	210.42	-	659.60
38	3	231.27	5.44	6.74	S	11.13	-	231.26	***218.85***	210.88	-	660.99
39	3	238.80	5.47	6.98	S	7.53	-	238.79	***226.39***	218.42	-	683.59
40	3	239.69	5.47	7.01	S	21.29	-	239.68	***227.28***	219.30	-	686.26
41	3	243.37	5.49	7.13	S	3.69	-	243.36	***230.96***	222.99	-	697.32
42	3	245.97	5.50	7.22	S	2.60	-	245.96	***233.56***	225.59	-	705.12
43	3	246.27	5.50	7.23	S	7.08	-	246.26	***233.86***	225.89	-	706.00
44	3	247.24	5.51	7.26	S	23.23	-	247.23	***234.83***	226.85	-	708.91
45	3	259.90	5.56	7.68	S	12.66	-	259.89	***247.49***	239.51	-	746.89
46	3	264.52	5.57	7.83	S	4.62	-	264.51	***252.11***	244.13	-	760.75
47	3	273.02	5.61	8.12	S	8.50	-	273.01	***260.61***	252.64	6.78	793.03
48	3	301.15	5.70	9.06	S	28.13	-	301.14	***288.74***	280.77	34.91	905.56
49	3	312.91	5.74	9.46	S	11.76	-	312.90	***300.50***	292.53	46.67	952.60
50	2	327.68	5.79	9.96	S	327.67	-	***327.67***	315.26	307.29	61.43	1,011.66
51	2	331.48	5.80	10.09	S	3.80	-	***331.47***	319.07	311.10	65.24	1,026.87
-	4	{374.73}	-	-	EO	{61.82}	-	374.72	362.32	***354.34***	108.49	{1,199.86}
-	3	{374.73}	-	-	EO	{150.31}	-	374.72	***362.32***	354.34	108.49	{1,199.86}
-	2	{374.73}	-	-	EO	{43.25}	-	***374.72***	362.32	354.34	108.49	**{1,199.86}**
52	5	382.75	5.94	11.86	S	116.51	-	-	-	-	***116.51***	116.51
53	5	383.24	5.94	11.88	S	11.81	-	-	-	-	***117.00***	117.00
-	5	{619.73}	-	-	EO	{236.49}	-	-	-	-	***353.49***	{353.49}
		10,686.83	**278.58**									**34,016.49**

Notes: q: patient id; TOS: time on study on a common timeline; MVF: mean value function; T: event type; IAT: inter-arrival time; S: shipment; EO: end of observations for item q; Times in curl brackets excluded from summations; $\hat{\beta}$*: see main text.*

The remaining columns in Table 1 and 2 provide values for use in the following computations:

1. Checking data for trends: This is achieved by computing the following test statistics, known as Laplace or centroid test (Ascher, 1983):

$$U = \frac{\sqrt{12n}}{t_a}\left(\frac{\sum_{i=1}^{n} x_i}{n} - \frac{t_a}{2}\right) \quad (1)$$

where $x_1, x_2, \ldots, x_n$ are n observed recurrence times from a given item over a period of length t_a ($t_a \neq x_n$). A set of items can be tested aggregately as an "equivalent" single item. In this case the following values for use in (1) can be obtained from the layout shown in Table 2: $n = 53$; $\sum_{i=1}^{n} x_i =$ 34,016.49 ; $t_a =$ 1,199.86 (max cumulative age); and $U \cong 0.88$. The test score is positive and less than one, suggesting that, across the manufacturing jobs considered, the times between successive shipment events do *not* exhibit significant trend. While details are not shown here, patients dispensing events ($n = 81$) exhibit a negative trend ($U \cong -5.23$, significant at 0.5%).

2. Estimating the average number of events that is likely to occur at a given time: Event recurrence times can be modelled by continuous approximation using a mean value function (MVF). An NHPP is an example of parametric MVF often used to describe recurrence time data in the presence of trends – such as patient dispensing events in the illustrative case described here. An NHPP-based MVF is the rate of event occurrence $\hat{\lambda} X_{iq}^{\hat{\beta}}$ computed in Table 2. Maximum likelihood estimators $\hat{\lambda}$ and $\hat{\beta}$ are obtained by numerical approximation through the following procedure (Crow, 1990):

$$\hat{\lambda} = \frac{\sum_{q=1}^{k} N_q}{\sum_{q=1}^{k}\left(T_q^{\hat{\beta}} - S_q^{\hat{\beta}}\right)} \quad (2)$$

$$\hat{\beta} = \frac{\sum_{q=1}^{k} N_q}{\hat{\lambda}\sum_{q=1}^{k}\left(T_q^{\hat{\beta}} \ln T_q - S_q^{\hat{\beta}} \ln S_q\right) - \sum_{q=1}^{k}\sum_{i=1}^{N_q} \ln X_{iq}} \quad (3)$$

Through the combined use of Table 1 and 2, one obtains the necessary values to solve the equations: $\sum_{q=1}^{k}\left(T_q^{\hat{\beta}} - S_q^{\hat{\beta}}\right) \cong$ 3,532.39; $\sum_{q=1}^{k}\left(T_q^{\hat{\beta}} \ln T_q - S_q^{\hat{\beta}} \ln S_q\right) \cong$ 21,715.76; $\sum_{q=1}^{k} N_q = 53$; and $\sum_{q=1}^{k}\sum_{i=1}^{N_q} \ln X_{iq} \cong 278.58$. Since equations (2) and (3) cannot be solved in closed form, the estimator $\hat{\beta}$ is found iteratively by arbitrarily choosing an initial value β^* for use in equation (3), and then minimising $d = \hat{\beta} - \beta^*$ to a desired level of accuracy (e.g., $0 \leq d \leq 0.000001$). This can be accomplished using off-the-shelf solvers such as those commonly embedded in electronic spreadsheets. In the shipment order events example considered here, $\hat{\lambda} \cong 0.015$ and $\hat{\beta} \cong 1.121$ (which is close to 1 and hence consistent with the absence of trend highlighted by the Laplace centroid test). Conversely, for the patient dispensing event $\hat{\lambda} \cong 0.076$ and $\hat{\beta} \cong 0.698$. These values underpin the curves shown in the upper half of Figure 2.

3.2. Findings from discrete-event simulation

For the sake of simplicity, the developed model is *informally* described, making reference to widely-used concepts in DES (Banks, 2010). The overall model is broken down in *modules* (collections of building-blocks) representing the streamlined CTSC considered here for illustrative purposes. Variables are referred to in squared brackets, details in the Appendix.

Clinical centre module: Figure 3 shows a clinical centre as it appears in an interactive visual simulation created using WITNESS. Underneath, an equivalent statechart visualisation is provided to illustrate the dynamic behaviour of the modelled entity 'patient', with an indication of its states. The system's behaviour is as follows. Patients enrol following staggered arrivals: in the absence of data on enrolment, the time between consecutive events is approximated through a random uniform variable [*v01*]. The total number of patients to enrol is a random variable [*v02*] set when the model is initialised. In reality, some centres might fail to enrol patients. A fixed time window [*v03*] and a random delay [*v04*] separate the start of the clinical study from the start of IMP production. Once enrolled, the patient can be in only to states: either at the clinic, or away. When at the clinic, the patient is either served if the IMP inventory on hand allows dispensing, or not served in case of shortage. The amount of time a patient spends away from the clinic is a random variable consistent with the distribution of inter-recurrence times in the field data [*v05*]. For each patient, this variable is updated each time a visit is completed. A simplification had to be introduced at this point because the nonstationary process for dispensing events discussed in the previous section could not be used 'as is' in the chosen DES software tool. While not ideal, probability density functions (pdf) were fitted to the inter-recurrence times, instead. Maximum-likelihood estimators for the parameters of three alternative pdfs were determined using the MASS package (Venables and Ripley, 2002) for the statistical programming language R (R Development Core Team, 2008). The results are shown in Figure 4 along with the significance of the Kolmogorov–Smirnov (K-S) goodness-of-fit test associated with them.

Manufacturing site module: In the current-state scenario, a pre-determined number of manufacturing job requests enter the model at consecutive, staggered times. The variability in the arrival of job requests [*v07*], in the processing and release of individual jobs [*v08*] is informed by the descriptive analysis of field data summarised in Figure 5. Upon completion, each jobs is available to fulfil shipment orders, and assigned the following attributes: 1) a shelf life expressed in days, randomly generated based on an observed range [*v09*]; and 2) an indication of the country for which it is released (for simulation purposes, each job has equal probability of being released for either clinical centre). These attributes are inherited by the simulation entities representing the individual IMP kits included in each job, the number of which is a random variable sampled form an empirical distribution [*v10*]. To simulate inventory build-up dynamics, IMP kits are held in lists (buffers) within each module. The residual useful life of each kit residing in a list is updated after a maximum residence time elapses (one day): if the expiry date for the corresponding lot is sufficiently distant, the kit is kept in the list; otherwise it is marked as expired and moved in a separate list and disposed of. The kits on hand are matched with shipment orders from the clinics as they arrive. In the base-case scenario, the

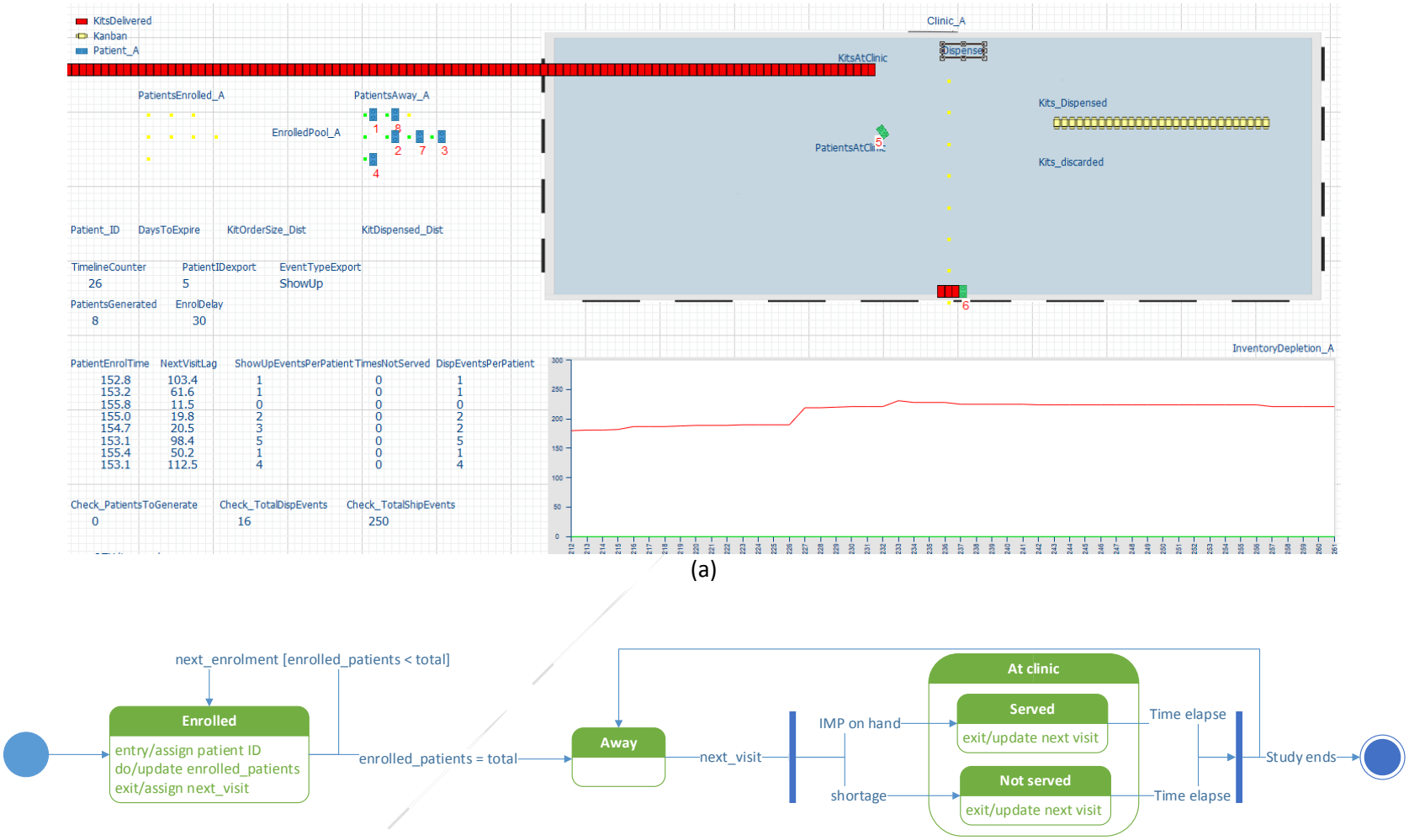

Figure 3. Example module for a clinical centre - screenshot from WITNESS dynamic display (a); Statechart-type equivalent view for the patient entity (b)

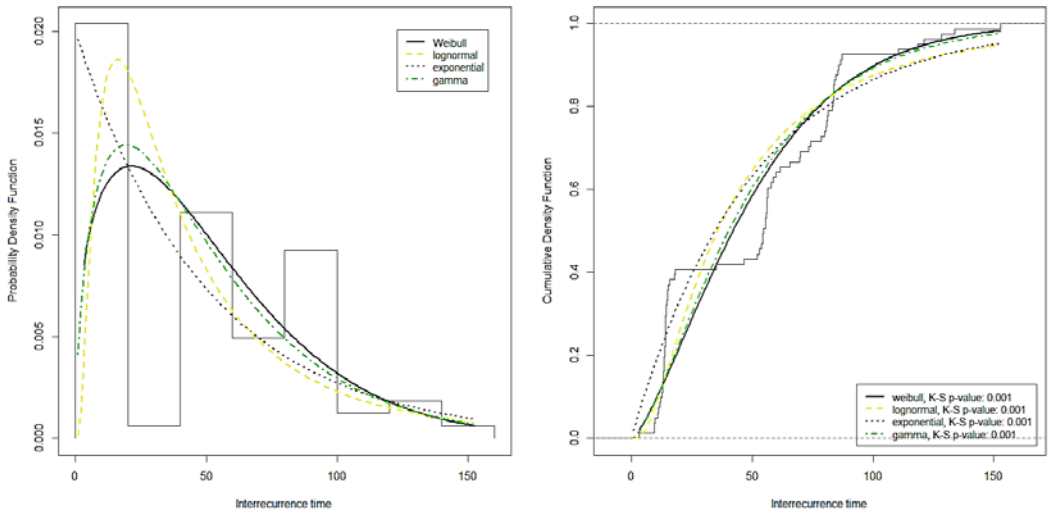

Figure 4. Fitting probability density functions to inter-recurrence time data for dispensing events

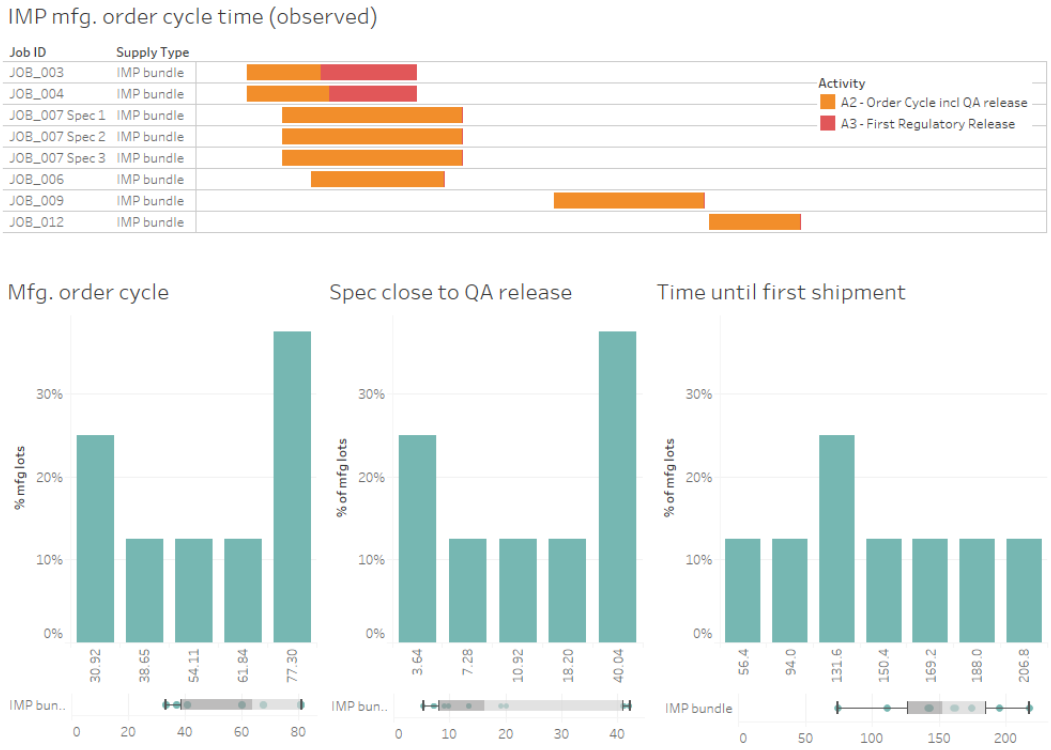

Figure 5. Visual summary of variability in manufacturing cycle time data

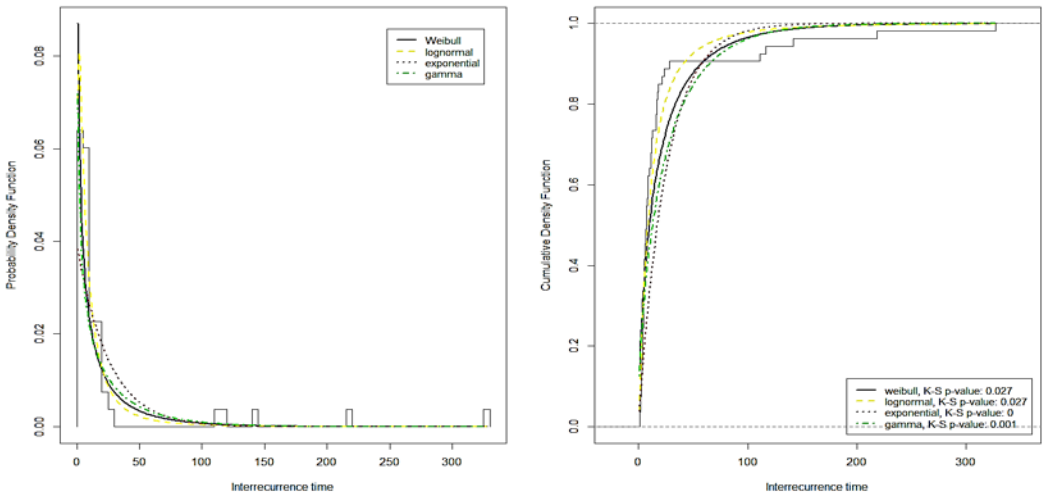

Figure 6. Fitting probability density functions to shipment orders interarrival times

arrival of shipment orders is characterised as follows: 1) orders arrive stochastically, following an interarrival times distribution [*v11*] fitted to the field data as shown in Figure 6: this was deemed appropriate because no significant trend was detected, and a lognormal distribution was chosen based on a K-S goodness-of-fit test; 2) the total number of orders arrival is fixed [*v12*], to reflect the observed data; 3) the first arrival [*v13*] is consistent with the study start date, considering possible delays; 4) the size of each order is sampled from an empirical distribution. The time it takes to processes and ship an order is sampled form an empirical distribution [*v14*] (the data does not suggest variation in order fulfilment and dispatch time with the size of an order).

Modules changes under a JIT scenario: While in the base-case scenario, shipment orders arrived at random based on evidence form empirical data, in a JIT scenario the clinics and the manufacturing modules are linked through a 'Kanban'-like replenishment system to operationalise a 'make-to-order' concept. Each clinical centre module replenishes its inventory by presenting to the manufacturing module a fixed-size withdrawal Kanban for the IMP [*v16*]. The first manufacturing run endows each clinic with initial inventory ahead of patient recruitment, whereas the follow-up runs are pulled by demand: as patients are recruited and the IMP is dispensed to them, the inventory on hand at clinic falls below a fixed level equal to the Kanban size, triggering replenishment. Upstream of the clinical centres modules, a hypothetical JIT clinical pharmacy with automated quality release responds to demand signals as they arrive (unlike the base-case). The estimated cycle time and throughput, with the associated variability, are estimated based on expert judgment based and prototype design. Comparison between the two scenarios is carried out by running both models for 900 time units, and perturbing the parameters listed underneath the column SA (Sensitivity Analysis) in the Appendix within a given range. For each combination, the model is run 5 times. The key response variables monitored were 1) number of times the patient was not served at any clinic due to IMP shortages (a state involving the simultaneous occurrence of a patient visiting the clinic, and no IMP kit

being on hand); and 2) number of kits disposed of because unused or expired at the end of the evaluation period. The results are summarised in Figure 7.

4. Discussion

Although with reference to a simplified numerical example, the previous section generates a combination of 'top-down' and 'bottom-up' insights into the behaviour of a CTSC, that help to address the initial *RQ* ("*To what extent would a JIT clinical pharmacy concept reduce unused inventory and improve service levels across a CTSC?*"). Overall, the simulation experiments suggest that the JIT concept provides consistently lower level of unused inventory across all experimental runs, as well as, reduced variability of the response in terms of unused inventory to perturbation in simulation parameters (Figure 7, right-hand side). An independent-samples t-test was conducted to compare the mean values obtained under the base-case ($\mathrm{M} = 312.1$, $\mathrm{S.D.} = 119.7$) and JIT ($\mathrm{M} = 47.8$, $\mathrm{S.D.} = 21.35$) scenario, supporting the hypothesis of significantly higher unused inventory of waste in the former; $t(397.76)$, $p < 0.001$.

While based on limited evidence, a potential reduction in unused inventory or waste between 67% and up to over 80% is achievable, on average, based upon the preliminary assessment presented. For the illustrative example with two clinical centres, a Kanban size 10 generates best service response compared to lower and higher sizes but also higher variability in unused inventory. While the JIT scenario is associated to an overall improvement in lower bound of disservice to patients' range, the upper bound worsened off compared to the current state. In the base-case scenario, a reduction of the number of simulated manufacturing jobs also reduces unused inventory suggesting a possible overlapping area of performance with the other scenario. However, this option systematically worsens service (marks with darker colours in Figure 7, left-hand side). In the base-case scenario, disservice also occurs with both high and low unused inventory levels (darker marks on interval extremes). This might be due to fewer runs occurring far apart from dispensing, which might have a negative impact on shelf life.

Despite being widely-known in manufacturing, the JIT concept is relatively new in the CTSC, hence the academic research does not provide much guidance on this specific topic. In general, simulation is increasingly used to support CTSC design, although it is not as widespread as deterministic models (Abdelkafi *et al.*, 2009). Unlike previous works using simulation in CTSC, the findings presented here illustrate how the exploration of field data informs a DES model design; and some of the simplifying assumptions that might be necessary to implement the model through specific software platforms.

While it is intuitively evident that different choices in representing recurrence times may affect the overall outcome of a simulation, especially in the presence of trend, this point is seldom highlighted in the academic literature, and difficult to verify in the absence of bespoke analysis. Similarly, the impact of an IMP shelf life is seldom taken into account. Here, it is shown that this modelling aspect can be insidious as it potentially undermines otherwise effective inventory reduction strategies.

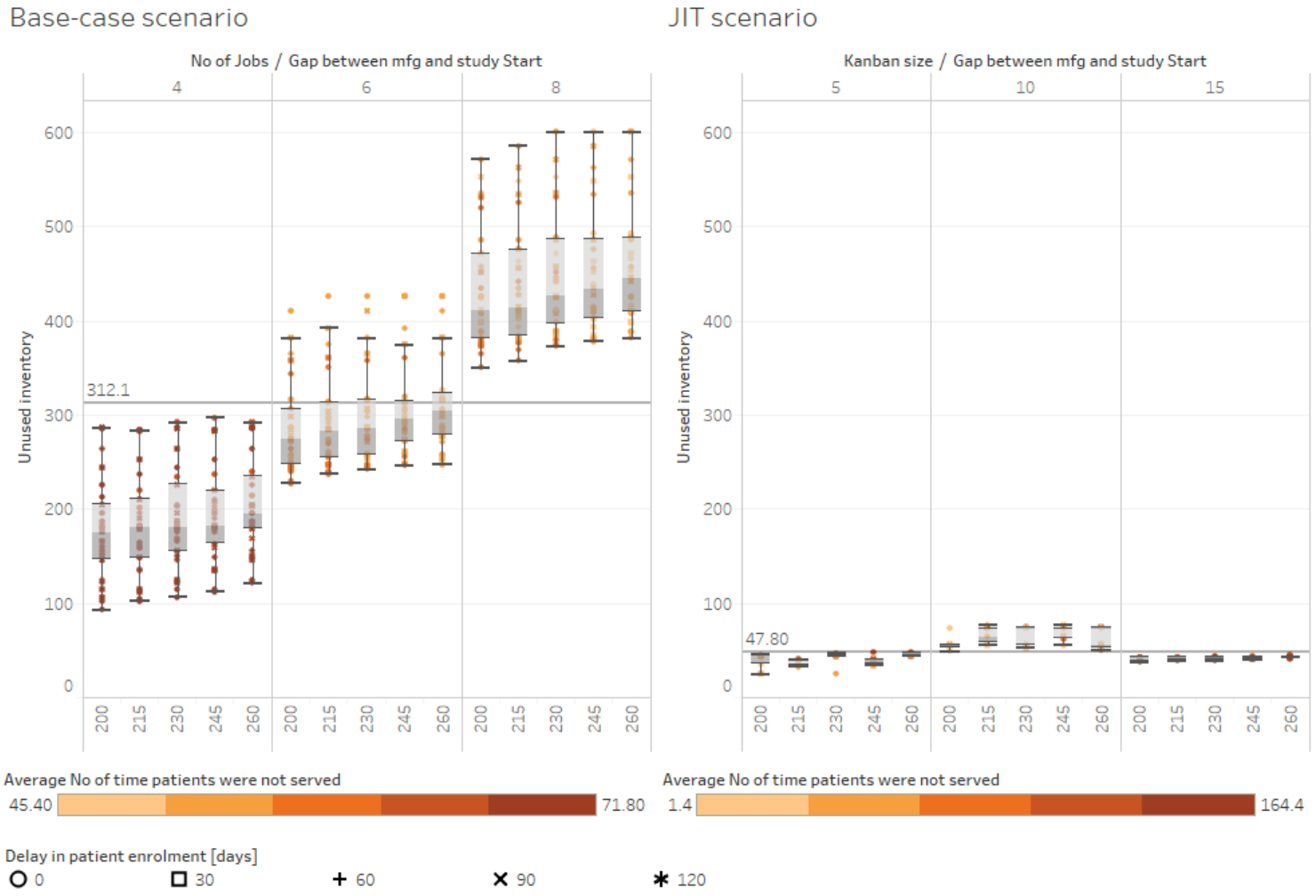

Figure 7. Visual summary of simulation experiments: base-case (left) and JIT scenarios (right)

5. Conclusion

This paper has proposed and illustrated a combination of CTSC field data analysis, and a proof-of-concept inventory profile simulation to evaluate alternative JIT manufacturing and distribution capabilities for an IMP. While a number of simplifying assumptions were made for illustrative purposes, the proposed combination of field data analysis and simulation is one of the few attempts to generate actionable knowledge from quantitative evidence that is typically available to businesses. Such knowledge can facilitate an otherwise challenging, 'ex-ante' evaluation emerging technologies such as the concept of JIT 'Automated Clinical Pharmacy'.

This research represents only an initial attempt to help assess the value proposition of having ultimate flexibility and late stage customisation in relation to the future needs/wants of clinical trial design. Further work aimed at validating and verifying key assumptions needs to be conducted through an iterative process of engagement with industry. While not meant for generalisation, preliminary results provide an initial feel for the necessary depth and breadth of analysis which is necessary to establish how automated and autonomous capabilities may fulfil the emerging needs of future clinical supply chain. Once scaled-up and refined, the analysis has potential to complement the technical advancements made by a leading pharmaceutical consortium.

Funding acknowledgment: Support from the Advanced Manufacturing Supply Chain Initiative (Grant No. 35708-233529, ReMediES – Reconfiguring Medicines End-to-end supply) is gratefully acknowledged.

References

Abdelkafi, C., Beck, Benoît H. L., David, B., Druck, C. and Horoho, M. (2009), "Balancing Risk and Costs to Optimize the Clinical Supply Chain—A Step Beyond Simulation", *Journal of Pharmaceutical Innovation*, Vol. 4 No. 3, pp. 96–106.

Anisimov, V.V. (2009), "Predictive modelling of recruitment and drug supply in multicenter clinical trials", in *Proceedings of the Joint Statistical Meeting*, 1-6 August 2009, Washington DC, USA.

Anisimov, V.V. and Fedorov, V.V. (2007), "Modelling, prediction and adaptive adjustment of recruitment in multicentre trials", *Statistics in Medicine*, Vol. 26 No. 27, pp. 4958–4975.

Ascher, H. (1983), "Discussion of 'point processes and renewal theory: a brief survey'", in Skwirzynski, J.K. (Ed.), *Electronic systems effectiveness and life cycle costing*, Springer-Verlag, Berlin, New York, pp. 113–117.

Banks, J. (2010), *Discrete-event system simulation*, Prentice Hall, Upper Saddle River, N.J.

[BMI] Business Monitor International Ltd (2017), *Global Pharmaceuticals & Healthcare Report - Q4 2017*, Business Monitor International, London.

Chen, Y., Mockus, L., Orcun, S. and Reklaitis, G.V. (2012), "Simulation-optimization approach to clinical trial supply chain management with demand scenario forecast", *Computers & Chemical Engineering*, Vol. 40, pp. 82–96.

Crow, L.H. (1990), "Evaluating the reliability of repairable systems", In *Annual Proceedings on Reliability and Maintainability Symposium*, 23-25 January, Los Angeles, CA, USA.

DHL (2017), *Improving supply chain visibility: How supply chain visibility can change the face of clinical trials*. Whitepaper, available at: www.dhl.com/supplychain

Fallon, D. and Browne, J. (1988), "Simulating Just-in-Time Systems", *International Journal of Operations & Production Management*, Vol. 8 No. 6, pp. 30–45.

Fleischhacker, A., Ninh, A. and Zhao, Y. (2015), "Positioning Inventory in Clinical Trial Supply Chains", *Production and Operations Management*, Vol. 24 No. 6, pp. 991–1011.

Friedli, T. (2006), *Operational excellence in the pharmaceutical industry*, Ed.-Cantor-Verl., Aulendorf (Germany).

Lamberti, M.J., Hsia, R., Mahon, C., Milligan, C. and Getz, K. (2016), "Assessing Global Clinical Supply Logistics", *Applied Clinical Trials*, Vol. 25 No. 10/11, pp. 26–28,30-34.

Made Smarter Review (2017). Available at https://www.gov.uk/government/publications/made-smarter-review [Accessed August 2018]

Paricio, I. (2016), "Smart Labels in the Clinical Trial Supply Chain", MSc Thesis, Delft.

R Development Core Team (2008), *R: A Language and Environment for Statistical Computing*, Vienna, Austria, available at: http://www.R-project.org.

Rees, H. (2011), *Supply Chain Management in the Drug Industry*, John Wiley & Sons.

Settanni, E., Newnes, L.B., Thenent, N.E., Parry, G., Sandborn, P., Bumblauskas, D. and Goh, Y.M. (2016), "Applying Forgotten Lessons in Field Reliability Data Analysis to Performance-based Support Contracts", *Engineering Management Journal*, Vol. 28 No. 01, pp. 3–13.

Strohhecker, J., Sibbel, R. and Dick, M. (2013), "Integrating Kanban principles in a pharmaceutical campaign production system", *Production Planning & Control*, Vol. 25 No. 15, pp. 1247–1263.

Terzi, S. and Cavalieri, S. (2004), "Simulation in the supply chain context: a survey", *Computers in Industry*, Vol. 53 No. 1, pp. 3–16.

Venables, W.N. and Ripley, B.D. (2002), *Modern applied statistics with S-Plus, Statistics and computing*, 4th ed., Springer, New York.

Appendix

Module/ Variable id	Description	Value or Expression				
		Base-case scenario	JIT scenario	Unit	SA*	Data pedigree
Clinic						
v01	Time between enrolments	Uniform (1,5)		[d]		Low
v02	Patients enrolled	Int. Uniform (5,12)		n.a.		Medium
v03	Study start	215		[d]	Y	Medium
v04	Delay in enrolment	30	As in base-case	[d]	Y	Medium
v05	Time until next visit	NegExp (50.13)		[d]		High
	Kits dispensed per visit	Empirical: 1-3 (90%); 4+ (10%)		[each]		High
Manufacturing						
	No of jobs	Pre-determined	Model output		Y	
v07	Time between job requests	Uniform (13,167)	Model output	[d]		Medium
v08	Mfg. order cycle time	Triangle (42,72,81)	Triangle (5,7,14)	[d]		High
v09	Shelf life	Triangle (217,369,500)	As in base-case	[d]		High
v10	Lot size (kits per job)	Empirical: 50-60 (50%), 80-100 (50%)	Empirical: 10-20 (90%); 21-40 (10%)	[each]		Low
v11	Time between ship. orders	Lnorm(1.224,2.142)	Model output	[d]		High
v12	Max order arrivals	300	Model output	n.a.	Y	High
v13	First arrival	V04 + V05	As in base-case	[d]		
v14	Shipment order size	Empirical: 4-16 (90%); 16-36 (10%)	see V16	[each]		High
v15	Time to fulfil order & dispatch	Empirical: 2-6 (83%); 6-10 (13%)	As in base-case	[d]		High
v16	Withdrawal Kanban, per clinic	n.a.	10	[each]	Y	Low
v17	Mfg. Kanban, per clinic	n.a.	10	[each]	Y	Low

*SA: values that are iteratively changed in the sensitivity analysis to test the simulation response