Principal-agent theory-based cost and reimbursement structures of isavuconazole treatment in German hospitals

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Summary

Background: Isavuconazole (ISA) is a frequently used antifungal agent for the treatment of invasive fungal diseases (IFDs). However, hospital reimbursement data for ISA is limited.

Objectives: The primary objective of this study was to analyse the different perspectives of relevant stakeholders and the (dis)incentives for the administration of ISA in Germany. To that aim, the health economic effects of using ISA from a hospital management perspective were analysed.

Patients/Methods: Based on principal-agent theory (PAT), the perspectives of (a) the patient (principal) as well as (b) physicians, (c) pharmacists and iv. hospital managers (all agents) were analysed. For the evaluation of the cost-containment and reimbursement strategies of ISA, the German diagnosis-related group (G-DRG) system was used.

Results: Hospitals individually negotiating additional payments for innovative treatment procedures (zusatzentgelte [ZE]) within the G-DRG system is a key element of hospital management for the reduction of total healthcare expenditure. Our analysis demonstrated the beneficial role of ISA in healthcare resource utilisation, primarily due to a shortened overall length of hospital stay. Depending on underlying disease, coded G-DRG and ISA formulation, large differences in total reimbursement and the amount of ZE was shown. The PAT demonstrated disincentives for hospital managers to use innovative drugs.

Conclusions: Based on the PAT, beneficial, detrimental and indifferent perspectives of different stakeholders regarding the usage of ISA were shown. A reduction of bureaucratic hurdles is needed in Germany for the extension of effective and innovative antifungal treatment strategies with ISA.

KEYWORDS
additional payments, antifungal treatments, aspergillosis, costs, G-DRG, hospital reimbursement, Invasive fungal diseases, isavuconazole, mycosis
1 | INTRODUCTION

Invasive fungal diseases (IFDs), such as invasive aspergillosis, are life-threatening infections with high mortality rates, and there has been an increasing incidence in recent years. The primary reasons behind fatal outcomes include the complexity and severity of the patient’s primary underlying disease, challenging diagnostic pathways and the potential side effects of currently available antifungal agents (such as nephrotoxicity). Current therapeutic regimens, depending on co-medication, comorbidities and risk factors, and which are recommended by national and international guidelines, include fluconazole, voriconazole, liposomal amphotericin B and/or isavuconazole (ISA).

ISA is a new triazole with a broad antifungal efficacy and is clinically equivalent to voriconazole, but with superior tolerability in the treatment of aspergillosis. ISA is an effective treatment option, particularly when voriconazole is contraindicated for QT prolongation, liver or kidney dysfunction or drug interactions.

In addition to the clinical burden of IFDs, recently published studies demonstrated high associated treatment costs. Policymakers, however, are obliged to contain their national healthcare expenditure, while healthcare costs in developed countries have been rising for years due to demographic changes, medical-technical progress and other causes. This raises common concerns that the quality of care may suffer, that is by delay or non-use of highly effective but more expensive treatments. Moreover, little is known about the specific effects of given cost-containment strategies on quality of care. Therefore, it is not clear whether the administration of new antifungal treatments is hampered by higher costs and/or cost-containment strategies. This is even less clear since new, higher-priced treatments seem to incur lower overall healthcare costs due to a reduced length of stay (LOS) in hospital, as an earlier study demonstrated for the usage of ISA.

Although this research is more than valuable, it has not clearly shown whether all perspectives of relevant stakeholders were included, or whether it covered only the hospital standpoint.

This study is focussed on the implementation of ISA reimbursement mechanisms for hospital providers. As innovative antifungals are typically used in the hospital setting, the aim is to investigate the influence of the ISA administration types on the cost-containment strategies and hospital reimbursement in Germany. Since national regulations of healthcare systems are quite complex and differ from each other, the space limitation of an article only allows us to display one system in detail. We chose Germany because it is the largest European market and will provide additional information for other European countries.

2 | MATERIALS AND METHODS

2.1 | Theoretical framework

The principal-agent theory (PAT) emerged in the 1970s and has previously been used to investigate similar questions in different settings, including health care. The origin of this theory is a matter of debate, but often Jensen and Meckling are cited. PAT played a major role in Bengt Holmström’s work and contributed to him winning the Sveriges Riksbank Prize in Economic Sciences in Memory of Alfred Nobel (often called the Nobel Prize in Economics) in 2016. PAT is used when economic subjects are limited in their decision-making (eg through asymmetrical information distribution). Incomplete information occurs when an individual appraises the actions of others. In a broad definition, there is a principal-agent relationship as soon as the well-being of one depends on the actions of the other. In a narrow definition, there is a client (principal) who, by mutual agreement, entrusts a contractor (agent) with a task for remuneration. Since the two may pursue different goals, conflicts can arise as the agent may take advantage of the information asymmetry to the detriment of the principal. The theory was extended far beyond economics or institutional studies to the context of information asymmetry, uncertainty and risk.

The treatment of IFDs is a typical application of PAT. A patient (principal) may rarely decide on her/his treatment due to the lack of information and/or knowledge. Instead, healthcare professionals (agents) will decide on her/his behalf. However, if one of the agents faces disincentives (eg because more effective treatment is more expensive and therefore not reimbursed), there may be reasons to decide on a treatment that is contrary to the principals’ interests. Figure 1 demonstrates our conceptual basis of PAT for the treatment setting.

To include multiple perspectives and comprehensive information, we considered three relevant healthcare professionals as agents for this PAT analysis: physicians, pharmacists and hospital managers. Based on common hospital workflows and the authors’ expertise, assumptions regarding the agents’ objectives were made. Figure 2 further demonstrates the relationship between the agents’ objectives to those of the principal.

2.2 | Costs and reimbursement

We analysed costs and reimbursement of ISA for the treatment of IFDs in German hospitals via a cost analysis. The German reimbursement for inpatient treatment (German diagnosis-related group [G-DRG] system) was analysed using publicly available groupers
(software that converts ICD-10 codes into G-DRG codes) and tariffs. The aim was to identify all G-DRGs relevant to ISA administration due to IFDs.

G-DRGs are coded based on the International statistical Classification of Diseases (ICD)-10 codes, main and side discharge diagnoses of patients, operation and procedure codes (OPS, www.dimdi.de)\textsuperscript{25,26} and current reimbursement handbooks provided by the Institute for the Remuneration System in Hospitals (InEK Siegburg, www.g-drg.de).\textsuperscript{27} Cost analysis that followed the hospital standpoint is based on the InEK cost matrix and was conducted by using the G-DRG Cost-tool, available via the G-DRG-Report-Browser (www.medinfoweb.de).\textsuperscript{24,28} In order to calculate the costs of ISA treatment, patients and G-DRGs were identified by the OPS codes 6-008g and 6-008h (ISA administration parenteral and oral) and based on the G-DRG handbook 2020.\textsuperscript{27} Following common base rates in Germany, we assumed that, at national level, the value of a G-DRG point was €3,500. No discounting of costs was performed because cost analysis stretches over a one-year timespan.\textsuperscript{24} Cost savings were calculated by multiplying data from the SECURE trial\textsuperscript{6} (reduced LOS of 2 days for ISA patients) and the (daily) cost information from the G-DRGs.

We calculated the related G-DRG reimbursements by the G-DRG handbook-determined cost weight of 2020 as an allocation basis of the costs of all regular cases with an average case-cost weight between the lower and upper limit of LOS. To determine G-DRG remuneration, we multiplied the different cost weights per G-DRGs with €3,500 as the value of a G-DRG point and included additional payments for inpatient hospital stay exceeding the G-DRG-specific threshold. To determine the ISA treatment reimbursement, we assumed a 45-day ISA treatment, with patients receiving a loading dose of 3 × 200 mg/day for the first two treatment days, and 1 × 200 mg for each following day for the treatment of invasive aspergillosis.\textsuperscript{5} Thereby, the official pricing, specified by Lauer Taxe reference list for pharmaceutical price information (www.lauer-fischer.de)\textsuperscript{29} was considered. By these amounts, we identified the additional payments for innovative treatment procedures (Zusatzentgelte [ZE]) for ISA per inpatient hospital stay.

For the reimbursement procedure, the focus was placed on hospitals that individually negotiated additional payments for ZE and new diagnostic and treatment methods (Neue Untersuchungs- und Behandlungsmethoden [NUB]) that are not yet covered by the G-DRG flat tariffs. Therefore, NUBs are usually the preliminary stage before being classified as ZE and eventually being considered in the G-DRG tariff. The aim of additional payments is to include innovative products (such as ISA) into everyday clinical routines. In our study, we referred to the additional payment of ISA as ZE, as ISA was classified as NUB in 2019\textsuperscript{30} and was changed by G-DRG handbook 2020 to ZE (ZE2020-166/167: administration of ISA, parenteral/oral).\textsuperscript{27} In the G-DRG system, ZE reimbursement is divided into (a) an individually negotiated reimbursement and (b) a nationwide reimbursement.

As the G-DRG reimbursement calculation is based on the average hospital costs, we used the G-DRG reimbursement as a proxy for a daily full cost in an inpatient setting.\textsuperscript{31} To evaluate the influence of cost-containment strategies on the quality of care, the relevant G-DRGs were analysed according to their average reimbursement, as well as their net effect with and without ZE, for ISA administration under consideration of LOS.

### 2.3 Ethics statement

No ethical approval was required for this study as the underlying data were retrieved from publicly available sources.
3 | RESULTS

3.1 | Principal-agent theory

Based on the author’s experience, four dimensions of potential (dis)incentives of ISA administration were identified: (a) medical outcomes, (b) treatment process, (c) treatment costs and (d) reimbursement (Table 1). Medical outcomes included the effectiveness of ISA for the treatment of IFDs. Our analysis showed that the incentives of the principal and all agents were aligned. Treatment process focused on treatment benefits and the reduction of adverse events. We found that principal and agent incentives were either aligned or indifferent (neutral). Reimbursement covered every type of remuneration of hospital care. Our analysis revealed that the incentives of the principal and agent (especially hospital managers) may (partially) diverge. The same was observed for treatment costs, which considered all costs associated with ISA treatment. Therefore, we have analysed reimbursement and treatment costs in more detail.

3.2 | Costs and reimbursement

Seven relevant G-DRG codes from the OPS code 6-008g (parenteral) were identified: A07B, A09B, A36A, A36B, E77B, R60C and R60D. Additionally, seven G-DRG codes from the OPS code 6-008h (oral) were found: A04D, A04E, E77B, E77D, R60B, R60C and R60D. Three of these G-DRG codes (E77B, R60C and R60D) were identified for both OPS codes.

In the OPS code 6-008g (parenteral), the overall ZE of €26 265 resulted from a 2-day loading dose of 3 × 200 mg/day followed by a single dose of 200 mg for 43 days for each G-DRG. The reference price for 200 mg parenteral ISA was €536/day. Two main findings resulted (Table 2). Firstly, due to the reduced LOS of 2 days, G-DRG cost savings occurred for each G-DRG, ranging from €963 in R60D to €2828 in A09B. Secondly, the total reimbursement (G-DRG + ZE) varied widely from €40 524 in E77B to €114 251 in A07B.

Considering the OPS code 6-008h (oral), the overall ZE of €5241 resulted from a 2-day loading dose of 3 × 200 mg/day followed by a single dose of 200 mg for 43 days for each G-DRG. The reference price for 200 mg oral ISA was €107/day. Our analysis yielded results similar to parenteral ISA administration (Table 3). Consequently, G-DRG cost savings were generated for each G-DRG code ranging from €694 in E77D to €2,184 in A04D. The total reimbursement (G-DRG + ZE) varied from €14 547 in E77D to €46 954 in A04D. Small cost savings and low reimbursement were identified in E77D for oral administration. The G-DRG code A04D, however, offered the highest cost savings (€2,184) and the highest total reimbursement (€46 954). To determine an ISA cost-reimbursement comparison, we conducted a sub-analysis for both OPS codes for the overlapping G-DRGs E77B, R60C and R60D. The sub-analysis identified specific cost shares for each G-DRG case referring to material cost (cost category group 4: drugs general and drugs individual) and thus, aimed to indicate the importance of ZE for hospital managers. Based on the InEK cost matrix, we calculated the accrual drug-cost shares within the G-DRGs (general/individual) to be €1070 in E77B, €2455 in R60C and €2821 in R60D.

### Table 1 Perspectives and (dis)incentives for the administration of ISA

| ISA effects                                      | Principal       | Agent          | Hospital manager |
|-------------------------------------------------|-----------------|----------------|-----------------|
| i. Medical outcomes                             |                 |                |                 |
| Fewer side effects                              | +               | +              |                 |
| Earlier discharge/shorter ICU stay              | +               | +              |                 |
| ii. Treatment process                           |                 |                |                 |
| No delay in clinical procedures                 | +               | +              | 0               |
| Therapeutic drug management                     | 0               | +              | 0               |
| Reduced LOS on specialised care units (eg ICU)  | +               | +              | 0               |
| iii. Treatment costs                            |                 |                |                 |
| Higher drug costs                               | 0               | 0              | 0               |
| Reduced LOS                                     | +               | +              |                 |
| iv. Reimbursement                               |                 |                |                 |
| Additional reimbursement (for high-quality care, | 0               | 0              | 0               |
| drug costs and other)                           |                 |                |                 |
| Reduced mechanical ventilation                   | 0               | 0              | +/–             |

Abbreviations: –, do not support the use of ISA; +/-, some effects are beneficial, others are detrimental; 0, indifferent; ICU, intensive care unit; ISA, isavuconazole; LOS, length of stay; PAT, principal-agent theory. +, support the use of ISA.
### TABLE 2  Cost and reimbursement structures of ISA (parenteral application, OPS code 6-008g)

| G-DRG code | Primary diagnosis (ICD-10) | Upper G-DRG threshold (days) | ALOS (days) | G-DRG reimbursement (cost weight × base rate) | 45-day G-DRG reimbursement | G-DRG cost savings/case through ISA (2 d) | Loading dose (2 d of 3 × 200 mg/d) | 43-day ISA reimbursement (Day 2 - Day 45) | Total reimbursement G-DRG + ISA |
|------------|-----------------------------|-------------------------------|------------|-----------------------------------------------|---------------------------|------------------------------------------|------------------------------------|-------------------------------------|----------------------------------|
| A07B       | J80.03, I21.4, I50.14       | 91                            | 72.9       | 87,986.50 €                                  | 87,986.50 €               | 2,413.90 €                               | 3,216.12 €                         | 23,048.86 €                        | 114,251.48 €                     |
| A09B       | J80.03, I31.4, I21.0        | 58                            | 57.3       | 81,021.50 €                                  | 81,021.50 €               | 2,827.98 €                               | 3,216.12 €                         | 23,048.86 €                        | 107,286.48 €                     |
| A36A       | C92.00, C83.3, C90.00       | 57                            | 38.6       | 40,495.00 €                                  | 40,495.00 €               | 2,098.19 €                               | 3,216.12 €                         | 23,048.86 €                        | 66,759.98 €                      |
| A36B       | T86.02, A46, C83.3          | 48                            | 29.6       | 25,532.50 €                                  | 25,532.50 €               | 1,725.17 €                               | 3,216.12 €                         | 23,048.86 €                        | 51,797.48 €                      |
| E77B       | B59, B25.0, J18.9           | 30                            | 15.1       | 7,315.00 €                                   | 14,259.00 €               | 968.87 €                                 | 3,216.12 €                         | 23,048.86 €                        | 40,523.98 €                      |
| R60C       | C92.00, C92.01, C92.50      | 40                            | 24.6       | 11,917.50 €                                  | 14,383.50 €               | 968.90 €                                 | 3,216.12 €                         | 23,048.86 €                        | 40,648.48 €                      |
| R60D       | C92.00, D46.2, C92.50       | 28                            | 13.5       | 6,503.00 €                                   | 14,504.00 €               | 963.41 €                                 | 3,216.12 €                         | 23,048.86 €                        | 40,768.98 €                      |

Note: Definitions of the G-DRG: A07B, Ventilation > 999 h or > 499 h with complex intensive care treatment > 4900/4600/4600 points, with complex OR procedure and ECMO from 384 h or with polytrauma or age < 16 y or complex intensive care treatment > 3220/– points; A09B, Ventilation > 499 h or >249 h with complex intensive care treatment > 2352/1932/2208 points, with attached misconception or tumour disease., age < 3 y or with high-complex procedures or with complex OR procedure or intensive complex treatment > 1764/1932/- P., age < 16 y; A36A, Intensive care complex treatment > 980/1104/-1565 effort points for certain diseases and disorders or intensive care complex treatment > 588/552/552 P. in case of failure and rejection of a graft of haematopoietic cells; A36B, Intensive care complex treatment > 588/552/828 and section 981/1105/1657 effort points for certain diseases and disorders or complicating constellation in case of failure and rejection of a graft of haematopoietic cells; E77B, Certain other infections and inflammations of the respiratory organs with certain CC or highly complex diagnosis or complex diagnosis for organ transplantation or intensive care complex treatment > 196/-/ effort points; R60C, Acute myeloid leukaemia with intensive chemotherapy, extremely CC or complex diagnostics when leukaemia or with moderate complex chemotherapy with certain complex factors or with extremely difficult CC with complex diagnostics or complex treatment. MDR with dialysis or extremely difficult CC or the heaviest CC; R60D, Acute myeloid leukaemia with intense chemotherapy, without complicated diagnosis, without dialysis, without port implantation, without ICU complex treatment. > 392/368/- effort points, without extremely difficult CC, without complex diagnosis when leukaemia or with dialysis or extremely severe CC (G-DRG-System, http://g-drg.de, last accessed 2020-03-19).

Abbreviations: ALOS, average length of stay; CC, complex constellation; ECMO, extracorporeal membrane oxygenation; G-DRG, German diagnosis-related group; ICD-10; ICU, intensive care unit; International statistical Classification of Diseases-10; ISA, isavuconazole; MDR, multidrug resistant pathogens; OPS, operation and procedure; OR, operating room (procedures).

*G-DRG handbook, 2020.
| G-DRG code | Main diagnoses (ICD-10) | Upper G-DRG threshold\(^a\) | ALOS (days)\(^a\) | G-DRG reimbursement (cost weight × base rate)\(^a\) | 45-day G-DRG reimbursement | G-DRG cost savings/case through ISA (2 d) | Loading dose (2 d of 3 × 200 mg/d) | 43-day ISA reimbursement (Day 2–Day 45) | Total reimbursement G-DRG + ISA |
|------------|-------------------------|-----------------------------|------------------|---------------------------------|--------------------------|---------------------------------|-------------------------------|--------------------------------|----------------------------------|
| A04D       | C92.00, C91.00, C93.00 | 56                          | 38.2             | 41,713.00 €                     | 2,183.93 €               | 641.74 €                        | 4,599.16 €                   | 46,953.90 €                     |
| A04E       | C92.00, C91.00, D46.2  | 51                          | 35.3             | 36,963.50 €                     | 2,094.25 €               | 641.74 €                        | 4,599.16 €                   | 42,204.40 €                     |
| E77B       | B59, B25.0, J18.0      | 30                          | 15.1             | 7,315.00 €                      | 968.87 €                 | 641.74 €                        | 4,599.16 €                   | 17,707.90 €                     |
| E77D       | J18.9, J18.1, J69.0   | 26                          | 13.3             | 4,616.50 €                      | 694.21 €                 | 641.74 €                        | 4,599.16 €                   | 14,547.40 €                     |
| R60B       | C92.00, C92.50, C92.80| 50                          | 32.3             | 17,916.50 €                     | 1,109.38 €               | 641.74 €                        | 4,599.16 €                   | 23,157.40 €                     |
| R60C       | C92.00, C92.50, C92.01| 40                          | 24.6             | 11,917.50 €                     | 968.90 €                 | 641.74 €                        | 4,599.16 €                   | 20,035.40 €                     |
| R60D       | C92.00, D46.2, C92.50 | 28                          | 13.5             | 6,503.00 €                      | 963.41 €                 | 641.74 €                        | 4,599.16 €                   | 20,311.90 €                     |

\(^a\)G-DRG handbook, 2020.

Note: Definitions of the G-DRG: A04D, Bone marrow transplantation/stem cell transfusion, allogeneic, with graft-versus-host disease Grade III and IV or except for plasmocytoma, HLA-different or with complex treatment in multi-resistant pathogens; A04E, Bone marrow transplantation/stem cell transfusion, allogeneic, except for plasmocytoma; E77B, Certain other infections and inflammations of the respiratory organs with certain CC or highly complex diagnosis or complex diagnostics for organ transplantation or intensive care complex treatment > 196/––/ effort points; E77D, Certain other infections and inflammations of the respiratory organs, age > 9 y; R60B, Acute myeloid leukaemia with intensive chemotherapy with complicated diagnosis or dialysis or port implantation or intensive care complex treatment > 392/368/– effort points or heaviest CC, age > 15 y; R60C, Acute myeloid leukaemia with intensive chemotherapy, extremely CC or complex diagnostics when leukaemia or with moderate complex chemotherapy with certain complicated factors or extremely difficult CC with complex diagnostics or complex treatment. MDR with dialysis or extremely difficult CC or the heaviest CC; R60D, Acute myeloid leukaemia with intense chemotherapy, without complicated diagnosis, without dialysis, without port implantation, without ICU complex treatment; > 392/368/– effort points, without extremely difficult CC without complex diagnosis when leukaemia or with dialysis or extremely severe CC (G-DRG-System, http://g-drg.de, last accessed 2020-03-19).

Abbreviations: ALOS, average length of stay; CC, complex constellation; G-DRG, German diagnosis-related group; HLA, human leucocyte antigen; ICD-10, ICU, intensive care unit; International statistical Classification of Diseases-10; ISA, isavuconazole; MDR, multidrug resistant pathogens; OPS, operation and procedure.
(Tables S1-S3). Thus, treatment costs were not fully reimbursed in any of the G-DRG cases, compared with the accrual costs of €26,265 for 45-day ISA parenteral treatment or €5241 for 45-day ISA oral treatment.

4 | DISCUSSION

Our study aimed to investigate the influence of two ISA formulations on cost-containment strategies and reimbursement of German hospitals. To our knowledge, this is the first analysis involving different perspectives of hospital stakeholders.

Compared with voriconazole, oral and parenteral ISA administration generated cost savings in each G-DRG code through shorter LOS. Due to respective G-DRG tariffs, total reimbursement (G-DRG + ZE) varied substantially from average G-DRG reimbursement.

More detailed analysis of innovative products (eg ZE) from a reimbursement perspective is needed. In Germany, ZE are required to reimburse innovative medical treatments that are not yet covered by G-DRG tariffs. However, consideration of ZE in clinical routines comes with immense bureaucratic burden and cost risks for hospital providers. Straight after InEK legitimising administration of an innovative product, hospital providers negotiate reimbursement with health insurance providers individually for each hospital. In contrast, purchase prices and conditions are negotiated separately between the hospital and pharmaceutical companies. Only if an agreement is achieved, the costs incurred by the innovative product will be covered by health insurance. If not, health insurance providers may refuse to pay, and costs are paid by the hospital providers. In such case, PAT demonstrates disincentives for hospital managers to use innovative drugs. Implementing innovative products into clinical routine bears cost risks for hospitals; however, hampering the utilisation of novel treatments may reduce the quality of care and clinical efficacy (as described recently). ZE or similar extra payment mechanisms are needed for innovative drugs which may help to align principals’ and agents’ incentives.

To shift the sole cost risk from hospital providers and to reduce the bureaucratic burden, the current triple-bilateral negotiation processes between (a) hospitals and health insurance providers, (b) hospitals and pharmaceutical companies and (c) health insurance providers with pharmaceutical companies (Figure 3) need to be reorganised towards a triangular structure that allows for transparent, performance- and outcomes-based cost-coverage, resulting in an adequate reimbursement for healthcare providers.

Merging negotiation processes for the purchase and reimbursement of drugs prevents cost risks for hospitals. Moreover, a trilateral agreement between all stakeholders could lead to efficient, transparent and quality-based cost-reimbursement structures supporting the timely arrival of innovative treatments and drugs into routine care.

**FIGURE 3** Triangular negotiation structure integrating ZE in daily clinical routine. The current triple-bilateral negotiation process between the hospital manager, health insurance provider and pharmaceutical company for integrating ZE in Germany. The arrows demonstrate the dependence of hospital managers on health insurance providers and pharmaceutical companies in a triple-bilateral structure. The dotted arrows demonstrate the relationship between hospital managers, health insurance providers and pharmaceutical companies in a triangular structure. PAT, principal-agent theory; ZE, zusatzentgelte

4.1 | Implications for future research

Our study outlined the relevance of a secured reimbursement of innovative but also expensive treatments, such as ISA, for hospital providers in Germany. Reorganisation of inefficient negotiation processes towards a triangular structure would yield multiple advantages: (a) less bureaucratic burden in general, including more rapid patient access to novel treatments, (b) efficient agreement on payments between all relevant stakeholders, allowing innovative treatments in inpatient care and (c) reduced cost risk for hospital providers.

In other European countries, there are fewer hurdles to overcome to obtain hospital reimbursement, or cost-covering mechanisms for innovative treatments already exist. For example, in Italy, pricing and reimbursement systems of pharmaceutical products are primarily based at a national level, resulting in less bureaucracy for hospital management.

In conclusion, our study has shown cost savings of using ISA for innovative but also expensive treatments, such as ISA, for hospital providers in Germany. Reorganisation of inefficient negotiation processes towards a triangular structure would yield multiple advantages: (a) less bureaucratic burden in general, including more rapid patient access to novel treatments, (b) efficient agreement on payments between all relevant stakeholders, allowing innovative treatments in inpatient care and (c) reduced cost risk for hospital providers.

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AUTHOR CONTRIBUTION
Florian Kron: Conceptualization (lead); Data curation (equal); Formal analysis (lead); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (lead); Supervision (lead); Validation (equal); Writing-original draft (lead); Writing-review & editing (equal). Sebastian Wingen-Heimann: Conceptualization (equal); Data curation (lead); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (lead). Julia Jeck: Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (lead); Project administration (equal); Resources (equal); Supervision (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). Carlo Lazzaro: Data curation (equal); Formal analysis (equal); Investigation (equal); Resources (equal); Validation (equal); Writing-review & editing (equal). Oliver A. Cornely: Methodology (equal); Supervision (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal).

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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