OPEN ACCESS

Nursing Students' Perceptions Of Simulation-Based Learning In Santa Elena, Ecuador

Vanessa Guadalupe Potosí-Chuquín¹, Carmen Obdulia Lascano-Espinoza², Carlos Efraín Andrade³, Sonnia Apolonia Santos-Holguín²

¹Facultad de Medicina, Salud y Deportes, Universidad Europea, Madrid, Spain. E-mail: 223f6980@live.uem.es (Corresponding author)

²Facultad de Ciencias Sociales y de la Salud, Universidad Estatal Península de Santa Elena, La Libertad, Ecuador. E-mail: clascano@upse.edu.ec

³Facultad de Sistemas y Telecomunicaciones, Universidad Estatal Península de Santa Elena, La Libertad, Ecuador. E-mail: candrade5130@upse.edu.ec

²Facultad de Ciencias Sociales y de la Salud, Universidad Estatal Península de Santa Elena, La Libertad, Ecuador. E-mail: ssantos@upse.edu.ec

Abstract

Introduction: Simulation-based learning is a fundamental component in the pedagogy of health sciences, as it facilitates the recreation of authentic clinical scenarios in a controlled setting. It facilitates the integration of theoretical knowledge, the development of clinical and interpersonal skills, the enhancement of reflective decision-making processes, and the resolution of conflicts, thereby ensuring the delivery of quality care. Objective: To analyze the perception of undergraduate nursing students in the province of Santa Elena, Ecuador, about simulation-based learning and its impact on their professional training. Methodology: This quantitative research, with a descriptive and inferential cross-sectional design, used an adapted and validated questionnaire, applied to 100 students. The instrument facilitated the collection of key information regarding their experiences and perceptions of simulation-based learning. Results: Seventy-seven percent and 7% of the students exhibited a neutral and negative perception of this methodology, respectively, which may reflect a perceived disconnection between the simulation and its purported benefits. Furthermore, 36% of respondents with prior experience indicated that their continued utilization of the methodology could potentially impact their communication skills with patients. However, the confidence interval indicates that this impact may be negligible or nonexistent. Conclusion: Although simulation-based learning is a primary tool for clinical learning, the results show the need for innovative strategies that optimize the development of competencies and improve their assessment among students. It is imperative to acknowledge the significance of customized approaches that are aligned with the specific requirements of the local context. These tailored methods are crucial not only as a desired enhancement but also as a grassroots strategy to optimize their impact in settings where resources are limited.

Keywords: nursing education; clinical competence; patient simulation; clinical decision making.

Resumen

Introducción: El aprendizaje basado en simulación es clave en la enseñanza de ciencias de la salud porque recrea escenarios clínicos reales en entornos seguros. Permite integrar conocimientos teóricos, desarrollar competencias clínicas e interpersonales, mejorar la toma de decisiones reflexivas y resolver conflictos, asegurando así una atención de calidad. Objetivo: Analizar la percepción de estudiantes de licenciatura en enfermería en la provincia de Santa Elena, Ecuador, sobre el aprendizaje basado en simulación y su impacto en su formación profesional. Metodología: Esta investigación cuantitativa, con diseño transversal descriptivo e inferencial, utilizó un cuestionario adaptado y validado, aplicado a 100 estudiantes. El instrumento permitió recolectar información clave sobre sus experiencias y percepciones del aprendizaje basado en simulación. Resultados: El 77% y el 7% de los estudiantes mostraron una percepción neutral y negativa hacia esta metodología, respectivamente, lo que podría reflejar una desconexión percibida entre la simulación y sus beneficios. El 36% de aquellos con experiencia previa indicó

que su uso continuo podría afectar sus habilidades de comunicación con los pacientes, aunque el intervalo de confianza sugiere que este impacto podría ser mínimo o inexistente. **Conclusión:** Aunque el aprendizaje basado en simulación es una herramienta primordial para el aprendizaje clínico, los resultados evidencian la necesidad de estrategias innovadoras que optimicen el desarrollo de competencias y mejoren su valoración entre los estudiantes. Enfoques adaptados a las necesidades locales son importantes no solo como una mejora deseable, sino como una estrategia de base para maximizar su impacto en contextos con recursos limitados.

Palabras clave: educación en enfermería; competencia clínica; simulación del paciente; toma de decisiones clínicas.

Introduction

According to the International Association of Nursing for Clinical Simulation and Learning, simulation is defined as a process that replicates the essential aspects of real professional practice in a controlled environment through guided and interactive experiences. This approach is designed to facilitate the development of competencies, enhance practical skills, and improve patient safety (1). Within this paradigm, Simulation-Based Learning (SBL) has emerged as a key methodology in nursing education, enabling the ongoing development of professionals who are adept at making precise clinical decisions in settings that demand high precision and advanced competencies.

The SBL methodology in nursing is predicated on pedagogical frameworks that are informed by the principles of sociocultural constructivism, a theoretical framework that posits that learning is constructed collectively through social interaction and the cultural context (3). This approach integrates experiential learning, which allows students to acquire knowledge and skills through practice in simulated scenarios. The concept of the Zone of Proximal Development (ZPD) is another foundational aspect, as it delineates the extent to which a student can achieve independently and the extent to which they can achieve with the support of pedagogical tools such as simulation, which favor deeper learning (4).

The utilization of simulation as a conduit between theoretical knowledge and practical application is instrumental in facilitating the acquisition and refinement of technical competencies, in addition to the cultivation of soft skills such as effective communication, decision-making under pressure, critical reflection, and problem-solving. It is noteworthy that these exercises take place in a controlled and risk-free environment, thereby ensuring the safety of the participants.

Within the nursing domain, a diverse array of simulators is employed to cater to distinct training requirements. High-fidelity simulators, for instance, meticulously and realistically replicate vital functions, while low-fidelity simulators facilitate the rehearsal of specific skills such as punctures or cardiopulmonary resuscitation. Additionally, simulated patients, portrayed by actors, generate a wide range of clinical scenarios, thereby enhancing the learning experience. Electronic simulation tools, including virtual and augmented reality, offer immersive three-dimensional environments, while mixed simulation combines different modalities to maximize educational outcomes (5,6).

In Ecuador, interest in the SBL has grown since 2000, with an initial focus on anatomical models (5). According to the findings of a 2017 study, the Inter-Andean region has the highest adoption rate of simulation equipment (29%), followed by the Littoral region (12.5%), while the Amazon region exhibits a notable absence of such resources in its institutions. These developments are indicative of a growing commitment to enhancing patient safety and the quality of clinical training through the increased implementation of simulators in Ecuador in recent years (7).

Nevertheless, research on the perception and effectiveness of SBL remains limited, particularly in resource-constrained contexts such as Ecuador. In this context, the Nursing degree program at Universidad Estatal Península de Santa Elena (UPSE), located in the Litoral region of Ecuador, has incorporated the SBL into its academic curriculum, supported by a Simulation Laboratory Practice Guide. The objective of this study is to explore the perception of nursing students of this

institution about the SBL to identify areas for improvement and adjust pedagogical strategies to better meet their training needs.

Methodology

The study adopted a quantitative approach with a cross-sectional, descriptive, and inferential design and this research was carried out in the undergraduate program in Nursing of the Faculty of Social and Health Sciences at UPSE, with the authorization of the director of the program. The study population included nursing students enrolled during the second academic period of 2024, corresponding to the months of August to December.

The inclusion criteria encompassed students enrolled in the aforementioned period who were engaged in academic levels incorporating simulation practices and who demonstrated a willingness to partake in the study. Conversely, students who did not sign the informed consent form were excluded from the study. To identify potential gaps among participating students as well as biased perceptions about their previous SBL-related experiences, a specific question was included in the first section of the survey, called "sociodemographic data." This inquiry sought to ascertain whether the students had prior experience with simulation practices or workshops related to SBL. This approach was adopted to ensure the collection of comprehensive and accurate data, thereby providing a more precise overview of the participants' perceptions.

Non-probabilistic convenience sampling was employed to select a sample of 100 students for participation in the study. The sample size was determined based on the availability of participants during the academic period, without a formal calculation due to the nature of the sampling. Data collection was carried out in person at the faculty's facilities, with researchers directly applying the surveys to nursing students. The instrument employed was an adaptation of a questionnaire developed by Yadav et al. (8), whose validity was established by the authors of the study with the collaboration of nursing experts. For this study, some items of the instrument were adapted to the context of the participants, and the final version was organized into two sections: the first dedicated to sociodemographic data and the second with 13 items on perceptions of SBL, assessed using a Likert scale that included the following response options: strongly disagree with 1 point, disagree with 2 points, neutral with 3 points, agree with 4 points, and strongly agree with 5 points. Subsequently, according to the scale of the original reference study (8), the scores were classified into three categories: unfavorable perception (scores between 15 and 35), neutral perception (between 36 and 55), and favorable perception (between 56 and 75).

To evaluate the reliability of the instrument, the questionnaire was administered to a group of 20 nursing students who were not part of the study. The Cronbach's alpha coefficient, a measure of internal consistency, was calculated to be 0.824, indicating a satisfactory degree of reliability. This finding substantiates the instrument's capacity to coherently assess perception, thereby ensuring its reliability.

The data collected were then subjected to analysis using IBM SPSS® statistical software (version 29.0.0.0) and Microsoft Excel®. Descriptive statistics were used to analyze the sociodemographic data and perceptions of the participants. Furthermore, Student's t-test was employed to compare the perceptions of students with and without simulation experience, considering a significance level of p < 0.05.

Ethical Considerations

This study was conducted in accordance with the ethical principles of autonomy, confidentiality, and justice. Participation was voluntary and informed, and only those who explicitly consented to the survey continued with it. The participants were informed about the objectives of the research, the anonymization of the data collection, and the possibility of withdrawing at any time without repercussions.

The firm adhered to the principles of Ecuador's Organic Law on the Protection of Personal Data and Article 66, paragraph 19, of the Constitution of the Republic of Ecuador, ensuring the confidentiality and privacy of the data. Given the anonymous nature of the survey, no personal identifiable information was gathered.

Results

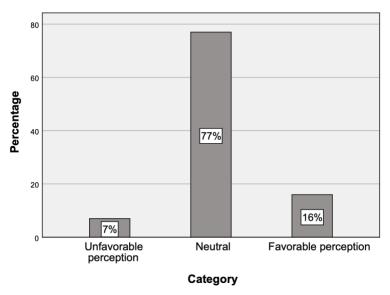
The study was developed with a sample of 100 nursing students, with no losses or exclusions during the data collection process. The demographic data presented in Table 1 indicates that 49% of the participants were in the 18 and 20 age range. The distribution of participants by gender was notable, with 73% of respondents identifying as female compared to 27% male. The distribution of respondents by semester of study is shown in Table 2. The majority (69%) of respondents were in an intermediate stage of their undergraduate program studies in Nursing. With respect to engagement in SBL-related workshops or seminars, 62% of students reported no prior participation, while only 36% indicated previous experience in simulations.

Table 1. Frequency distribution of demographic characteristics and simulation experience.

Feature		Frequency	Percentage
	18 to 20 years old	49	49%
Age	21 to 23 years old	33	33%
	Over 24 years	18	18%
Sex	Male	27	27%
	Female	73	73%
Semester	Third	27	27%
	Room	42	42%
	Sixth	31	31%
Previous attendance at an	Yes	38	38%
SBL workshop/seminar	No	62	62%
Previous simulation	Yes	36	36%
experience	No	64	64%

In addition to demographic characteristics, Figure 2 shows that most nursing students, represented by 77%, maintained a neutral stance regarding the SBL methodology. 16% of the participants perceived SBL favorably, while 7% perceived it unfavorably.

Figure 1. Distribution of nursing students' perception of SBL.



Finally, Table 2 presents the results of Student's t-test. This table compares the perceptions of students with and without previous experience in simulation by evaluating 13 items related to SBL in their training. Of these items, 12 did not show statistically significant differences between the two groups, with *p*-values greater than 0.05.

However, item 11, which asked whether the constant use of SBL causes a deterioration in communication skills with patients, showed a statistically significant difference of (p = 0.047). On the other hand, the confidence interval, which covers a range of values from -0.07 to 0.92, suggests that the effect of SBL on students' communication skills is not completely clear or uniform and could range from a small impairment to an improvement.

Table 2. Student's t-test results: comparison of perceptions about SBL between students with and without previous experience.

Items	<i>p</i> -value	95% Confidence interval
1. Can simulation support the development of clinical skills?	0.088	-0.14 a 0.75
2. Will SBL help increase students' confidence levels when dealing with real patients?	h 0.293	-0.60 a 0.34
3. Do you think SBL can be used as support in clinical practice and not as a substitute for it?	0.220	-0,27 a 0,62
4. Do you think SBL can create a very realistic, safe, and reproducible learning environment?	0.312	-0.35 a 0.59
5. Do you think the importance of ethical issues will be reduced with the repeated use of SBL?	0.099	-0.16 a 0.75
6. Do you think SBL will minimize the empathy of professionals towards patients?	0.484	-0.52 a 0.54
7. Do you think SBL can improve patient safety?	0.457	-0.42 a 0.47
8. Do you think SBL can replace living patients in a practical exam?	0.159	-0.27 a 0.81
9. Do you think SBL will hinder the team's efforts by minimizing role identity in an emergency?	0.071	-0.11 a 0.77
10. Do you think that repeated practice of the procedure in the SBL wil improve the user's performance?	¹ 0.195	-0.23 a 0.58
11. Will the constant use of SBL lead to a deterioration in communication skills with patients?	0.047	-0.07 a 0.92
12. Can simulation help to see and manage even the rarest cases in nursing?	0.360	-0.34 a 0.50
13. Do you think SBL will reduce stress in the learning environment?	0.240	-0.30 a 0.64

Discussion

Previous research has demonstrated the merits of SBL, including its capacity to enhance the quality of training and reduce the time required for students to develop clinical competencies and professional skills (9). However, the present study found that more than 75% of the students expressed a neutral perception of simulation, which could be related to biased perception

of previous simulation experiences, a possible lack of follow-up or use of simulation practices, limitations in the implementation of SBL models, or low attendance at SBL workshops (Table 1). The extant literature suggests that students' perceptions are influenced by the quality and realism of simulations; the greater the similarity to real situations, the greater the motivation and effectiveness in learning (8,10). However, this realism is not solely dependent on advanced technology; the rigor of preparation and the expertise of teachers also play a significant role (11,12).

Despite the institution's investment in simulation laboratories and a comprehensive instructional guide for simulative learning, the low positive perception of SBL in this study underscores the necessity for a re-examination of current methodologies to enhance their effectiveness (13). To achieve this, it is essential that simulations transcend technical practice and evolve into the development of a comprehensive skill set, encompassing communication, critical thinking, decision-making, and teamwork. In this regard, role-playing simulations, in which nurses and patients engage in collaborative scenarios, have been identified as a promising approach. These kinds of simulations facilitate the rehearsal of patient-centered care scenarios, promoting the development of real-time problem-solving and decision-making skills.

To this end, it is imperative that educators possess not only technical expertise but also pedagogical aptitude, allowing them to meticulously design effective simulations, facilitate critical reflections, and adapt to pragmatic methodologies (14,15). This underscores the importance of teacher training in educational models and strategies that favor the integration of SBL in the teaching-learning process (16).

In this regard, the Miller Pyramid model emerges as a potentially valuable instrument, enabling the systematic development of competencies, from theoretical understanding to practical application in authentic settings (17). While the model was originally developed for the evaluation of medical professionals, its principles can be adapted to organize training into four distinct levels: know (theoretical knowledge), know how (application of knowledge), demonstrate how (practice in simulated environments), and do (execution in real scenarios). In the SBL, this model could be reinterpreted as a continuous cycle that allows students to delve deeper into each level as they face new clinical situations and greater complexity in patient care.

Furthermore, the synergistic implementation of complementary strategies, such as pre-briefing and debriefing, is instrumental in ensuring the success of SBL (1). Pre-briefing has been shown to equip students with a clear understanding of the exercise's purpose, the roles they are to assume, and the skills to be evaluated (2). Conversely, debriefing facilitates a subsequent critical reflection that allows performance to be reviewed, strengths and areas for improvement to be identified, and learning to be consolidated through feedback (5,15).



Figure 2. Adaptation of Miller's Pyramid as a feedback loop in SBL (17).

• Direct patient care

Demonstrate how

• Practice with simulation

Educators may also adopt a case study—based pedagogical approach, thereby addressing multiple interrelated dimensions of care (13). In the biological aspect, emphasis can be placed on knowledge about anatomy, physiology, and pathologies. In the psychological domain, the use of simulations can foster empathy and communication skills. The integration of sociocultural dimensions can be facilitated using scenarios that illustrate how patients' beliefs and values influence their health status. Finally, bioethical aspects can be addressed by applying the four associated principles, such as autonomy, beneficence, non-maleficence, and justice (13).

However, a notable contrast emerges from the findings of one-third of students with prior simulation experience. These students reported that consistent utilization of this methodology could have a deleterious effect on their communication skills with patients. This observation stands in contrast to the findings reported in previous research (8,10,12).

While the *p*-value indicates substantial differences between students with and without prior simulation experience, the confidence interval suggests that the impact of SBL on communication may range from a mild deterioration to a substantial improvement or even be negligible. These variations could be attributed to factors such as i) personal motivation, ii) students' previous experiences with SBL, iii) the quality of the simulations, and iv) the methodology implemented by the institution.

Finally, optimizing SBL involves overcoming challenges such as the allocation of resources for high-fidelity laboratories and the formulation of comprehensive strategies that integrate soft skills, technical expertise, and clinical procedures to enhance the training of future nursing professionals.

Conclusions

In summary, 77% of the students exhibited a neutral perception, while 7% expressed an unfavorable perception towards simulation-based learning. This could reflect, in most respondents, a perceived disconnect between this methodology and its training benefits. This attitude underscores the necessity of integrating innovative pedagogical strategies that enhance both the perception and impact of simulation on the development of competencies.

Conversely, 36% of students with prior experience indicated that continued use of SBL could affect their communication skills with patients. However, statistical analyses suggest that this impact would be minimal or even non-existent. These findings underscore the necessity to fortify the pedagogical approach to SBL, incorporating strategies that foster the cultivation of both technical competencies and interpersonal skills, which are paramount for the clinical milieu.

While many institutions worldwide invest in high-fidelity simulators to recreate realistic clinical experiences, in Ecuador, it is important to prioritize accessible alternatives that optimize existing resources. The implementation of such solutions would overcome economic constraints and respond to local needs, thereby promoting the development of practical skills through creative and holistic approaches.

The implementation of accessible SBL methodologies, in conjunction with teacher training on the efficient use of resources, has the potential to serve as an effective strategy for enhancing student learning. The efficacy of simple and collaborative methods has been demonstrated, obviating the necessity for advanced simulators. Likewise, the execution of pilot projects involving educators and health professionals could generate simulation experiences more aligned with local realities and facilitate the updating of the academic curriculum to better prepare students.

In conclusion, an SBL that is strategically adapted to local conditions has the potential to transform nursing education in Ecuador and strengthen both technical competencies and the comprehensive preparation of students to face the challenges of the current clinical environment.

References

- 1. Watts PI, Rossler K, Bowler F, Miller C, Charnetski M, Decker S, et al. Onward and Upward: Introducing the Healthcare Simulation Standards of Best PracticeTM. Clin Simul Nurs [Internet]. 2021 Sep 1 [cited 2024 Dec 4];58:1–4. Available from: http://www.nursingsimulation.org/article/S1876139921000931/fulltext
- 2. Koukourikos K, Tsaloglidou A, Kourkouta L, Papathanasiou I V., Iliadis C, Fratzana A, et al. Simulation in Clinical Nursing Education. Acta Informatica Medica [Internet]. 2021 [cited 2024 Oct 25];29(1):15. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8116070/
- 3. Morales LG, Martínez VB, Olarte EGT, Carvajal D. Prácticas y estrategias didácticas en el modelo pedagógico constructivista en enfermería. Revista Repertorio de Medicina y Cirugía [Internet]. 2022 Jun 23 [cited 2024 Dec 5];31(1):52–7. Available from: https://revistas.fucsalud.edu.co/index.php/repertorio/article/view/1097/1870
- 4. Piña-Jiménez I, Amador-Aguilar R. La enseñanza de la enfermería con simuladores, consideraciones teórico-pedagógicas para perfilar un modelo didáctico. Enfermería Universitaria. 2015 Jul 1;12(3):152–9.
- 5. Pastuña-Doicela R, Segovia-Hernandez R, Alvarado-Alvarado A, Núñez-Garces A, Pastuña-Doicela R, Segovia-Hernandez R, et al. Simulación clínica virtual en enfermería en tiempos de pandemia: Percepción de estudiantes. Investigación en educación médica [Internet]. 2023 Oct 1 [cited 2024 Sep 22];12(48):52–63. Available from: http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S2007-50572023000400052&lng=es&nrm=iso&tlng=es
- 6. Juguera Rodríguez L, Díaz Agea JL, Pérez Lapuente ML, Leal Costa C, Rojo Rojo A, Echevarría Pérez P. La simulación clínica como herramienta pedagógica: percepción de los alumnos de Grado en Enfermería en la UCAM (Universidad Católica San Antonio de Murcia). Enfermería Global [Internet]. 2014 [cited 2024 Sep 22];13(33):175–90. Available from: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1695-61412014000100008&lng=es&nrm=iso&tlng=es
- 7. L MJG, Aucatoma K, Piedrahita FM, Rivas A. La cultura de seguridad del paciente como estrategia para evitar errores médicos. Mediciencias UTA [Internet]. 2021 Jul 1 [cited 2024 Sep 22];5(3):32–41. Available from: https://revistas.uta.edu.ec/erevista/index.php/medi/article/view/1189
- 8. Yadav S, Kumar Dular S, Jyoti S. Perception of nursing students towards simulation-based education in nursing profession. ANVESAK [Internet]. 2022 Jun [cited 2024 Oct 24];52. Available from: https://www.researchgate.net/publication/362304024
- 9. Cooper S, Cant R, Porter J, Bogossian F, McKenna L, Brady S, et al. Simulation based learning in midwifery education: A systematic review. Women and Birth [Internet]. 2012 Jun 1 [cited 2024 Sep 29];25(2):64–78. Available from: https://pubmed.ncbi.nlm.nih.gov/21489894/
- 10. Tong LK, Li YY, Au ML, Ng WI, Wang SC, Liu Y, et al. The effects of simulation-based education on undergraduate nursing students' competences: a multicenter randomized controlled trial. BMC Nurs [Internet]. 2024 Dec 1 [cited 2024 Oct 25];23(1):1–15. Available from: https://bmcnurs.biomedcentral.com/articles/10.1186/s12912-024-02069-7
- 11. Broussard L. Simulation-Based Learning: How Simulators Help Nurses Improve Clinical Skills and Preserve. Nurs Womens Health [Internet]. 2008 Dec 1 [cited 2024 Sep 28];12(6):521–4. Available from: https://pubmed.ncbi.nlm.nih.gov/19121057/
- 12. Alrashidi N, Pasay an E, Alrashedi MS, Alqarni AS, Gonzales F, Bassuni EM, et al. Effects of simulation in improving the self-confidence of student nurses in clinical practice: a systematic review. BMC Med Educ [Internet]. 2023 Dec 1 [cited 2024 Sep 29];23(1):1–12. Available from: https://bmcmededuc.biomedcentral.com/articles/10.1186/s12909-023-04793-1
- 13. Piña-Jiménez I, Amador-Aguilar R. La enseñanza de la enfermería con simuladores, consideraciones teórico-pedagógicas para perfilar un modelo didáctico. Enfermería

- Universitaria [Internet]. 2015 Jul 1 [cited 2024 Sep 29];12(3):152–9. Available from: https://www.sciencedirect.com/science/article/pii/S1665706315000445
- 14. Chernikova O, Holzberger D, Heitzmann N, Stadler M, Seidel T, Fischer F. Where salience goes beyond authenticity. https://doi.org/101024/1010-0652/a000357 [Internet]. 2023 Jun 12 [cited 2024 Oct 22];38(1–2):15–25. Available from: https://econtent.hogrefe.com/doi/10.1024/1010-0652/a000357
- 15. Chernikova O, Heitzmann N, Stadler M, Holzberger D, Seidel T, Fischer F. Simulation-Based Learning in Higher Education: A Meta-Analysis. Rev Educ Res [Internet]. 2020 Aug 1 [cited 2024 Oct 22];90(4):499–541. Available from: https://journals.sagepub.com/doi/10.3102/0034654320933544
- 16. Ramírez FU. Simulación en el aprendizaje, práctica y certificación de las competencias en medicina. ARS MEDICA Revista de Ciencias Médicas [Internet]. 2007 Aug 7 [cited 2024 Sep 30];36(2):152–63. Available from: https://www.arsmedica.cl/index.php/MED/article/view/154
- 17. Miller GE. The assessment of clinical skills/competence/performance. Acad Med [Internet]. 1990 [cited 2024 Oct 28];65(9 Suppl):S63–7. Available from: https://pubmed.ncbi.nlm.nih.gov/2400509/